(*NEW SERIES.*)

No. 20.

SCIENTIFIC MEMOIRS

BY

OFFICERS OF THE MEDICAL AND SANITARY DEPARTMENTS

OF THE

GOVERNMENT OF INDIA.

SERUM-THERAPY OF PLAGUE IN INDIA;

REPORTS BY MR. W. M. HAFFKINE, C.I.E., AND VARIOUS OFFICERS OF THE PLAGUE RESEARCH LABORATORY, BOMBAY.

EDITED WITH AN INTRODUCTION

BY

LIEUT.-COL. W. B. BANNERMAN, M.D., B.Sc., F.R.S.E., I.M.S.,
Director, Plague Research Laboratory, Bombay.

ISSUED UNDER THE AUTHORITY OF THE GOVERNMENT OF INDIA BY THE SANITARY COMMISSIONER WITH THE GOVERNMENT OF INDIA, SIMLA.

CALCUTTA:
OFFICE OF THE SUPERINTENDENT OF GOVERNMENT PRINTING, INDIA.
1905.

No. 20.

(NEW SERIES.)

SCIENTIFIC MEMOIRS

BY

OFFICERS OF THE MEDICAL AND SANITARY DEPARTMENTS

OF THE

GOVERNMENT OF INDIA.

SERUM-THERAPY OF PLAGUE IN INDIA;

REPORTS BY MR. W. M. HAFFKINE, C.I.E., AND VARIOUS OFFICERS OF THE PLAGUE RESEARCH LABORATORY, BOMBAY.

EDITED WITH AN INTRODUCTION

BY

LIEUT.-COL. W. B. BANNERMAN, M.D., B.Sc., F.R.S.E, I.M.S.,

Director, Plague Research Laboratory, Bombay.

ISSUED UNDER THE AUTHORITY OF THE GOVERNMENT OF INDIA BY THE SANITARY COMMISSIONER WITH THE GOVERNMENT OF INDIA, SIMLA.

CALCUTTA:

OFFICE OF THE SUPERINTENDENT OF GOVERNMENT PRINTING, INDIA.

1905.

Agents for the Sale of Books published by the Superintendent of Government Printing, India, Calcutta.

IN ENGLAND.

H. S. KING & CO., 65, Cornhill, & 9, Pall Mall, London.
E. A. ARNOLD, 41 & 43, Maddox Street, Bond Street, London, W.
CONSTABLE & CO., 16, James Street, Hay Market, London, W.
P. S. KING & SON, 2 & 4, Great Smith Street, Westminster, London, S.W.
KEGAN PAUL, TRENCH, TRÜBNER & CO., Charing Cross Road, London, W.C.
BERNARD QUARITCH, 15, Piccadilly, London, W.
B. H. BLACKWELL, 50 & 51, Broad Street, Oxford.
DEIGHTON BELL & CO., Cambridge.

ON THE CONTINENT.

R. FRIEDLÄNDER & SOHN, 11, Carlstrasse, Berlin, N.W.
OTTO HARRASSOWITZ, Leipzig.
KARL W. HIERSEMANN, Leipzig.
ERNEST LEROUX, 28, Rue Bonaparte, Paris.
MARTINUS NIJHOFF, The Hague, Holland.

IN INDIA.

THACKER, SPINK & CO., Calcutta and Simla.
NEWMAN & CO., Calcutta.
S. K. LAHIRI & CO., Calcutta.
R. CAMBRAY & CO., Calcutta.
HIGGINBOTHAM & CO., Madras.
V. KALYANARAMA IYER & CO., Madras.
G. A. NATESAN & CO., Madras.
THACKER & CO., LD., Bombay.
A. J. COMBRIDGE & CO., Bombay.
D. B. TARAPOREVALA, SONS & CO., Bombay.
RADHABAI ATMARAM SAGOON, Bombay.
N. B. MATHUR, Superintendent, Nazair Kanun Hind Press, Allahabad.
RAI SAHIB M. GULAB SINGH & SONS, Mufid-i-Am Press, Lahore.
Superintendent, American Baptist Mission Press, Rangoon.
SUNDER PANDURANG, Bombay.
A. M. & J. FERGUSON, Ceylon.

List of Numbers of Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India (New Series) published previous to the present issue.

No. 1. Standardisation of Calmette's anti-venomous serum with pure cobra venom : the deterioration of this serum through keeping in India, by *Captain G. Lamb, I.M.S., and Wm. Hanna, Esq., M.B.* Price As. 3 or 4*d.*

No. 2. Malaria in India, by *Captain S. P. James, I.M.S.* Price Re. 1-8 or 2*s.* 3*d.*

No. 3. Some observations on the poison of Russell's Viper (Daboia Russellii), by *Captain G. Lamb, I.M.S., and Wm. Hanna, Esq., M.B.* Price As. 5 or 6*d.*

No. 4. On the action of the venoms of the Cobra and of the Daboia on the red blood corpuscles and on the blood plasma, by *Captain G. Lamb, I.M.S.* Price As. 8 or 9*d.*

No. 5. Specificity of anti-venomous sera, by *Captain G. Lamb, I.M.S.* Price As. 3 or 4*d.*

No. 6. First report on the anti-malarial operations in Mian Mir, 1901-03, by *Captain S. P. James, I.M.S.* Price As. 12 or 1*s.* 2*d.*

No. 7. Some observations on the poison of the Banded Krait (Bungarus Fasciatus), by *Captain G. Lamb, I.M.S.* Price As. 8 or 9*d.*

No. 8. A preliminary report on a parasite found in patients suffering from enlargement of the spleen in India, by *Lieutenant S. R. Christophers, I.M.S.* Price Re. 1-8 or 2*s.* 3*d.*

No. 9. Second report of the anti-malarial operations at Mian Mir, 1901-03, by *Lieutenant S. R. Christophers, I.M.S.* Price As. 10 or 1*s.*

No. 10. Specificity of anti-venomous sera (second communication), by *Captain G. Lamb, I.M.S.* Price As. 8 or 9*d.*

No. 11. On a parasite found in persons suffering from enlargement of the spleen in India—Second Report, by *Lieutenant S. R. Christophers, I.M.S.* Price Rs. 2 or 3*s.*

No. 12. On the Morphology, Teratology and Diclinism of the flowers of Cannabis, by *Major D. Prain, I.M.S.* Price As. 14 or 1*s.* 4*d.*

No. 13. Oriental or Delhi Sore, by *Captain S. P. James, I.M.S.* Price As. 10 or 1*s.*

No. 14. On a parasite found in the white corpuscles of the blood of dogs, by *Captain S. P. James, I.M.S.* Price As. 10 or 1*s.*

No. 15. On a parasite found in persons suffering from enlargement of the spleen in India—Third Report, by *Lieutenant S. R. Christophers, I.M.S.* Price As. 10 or 1*s.*

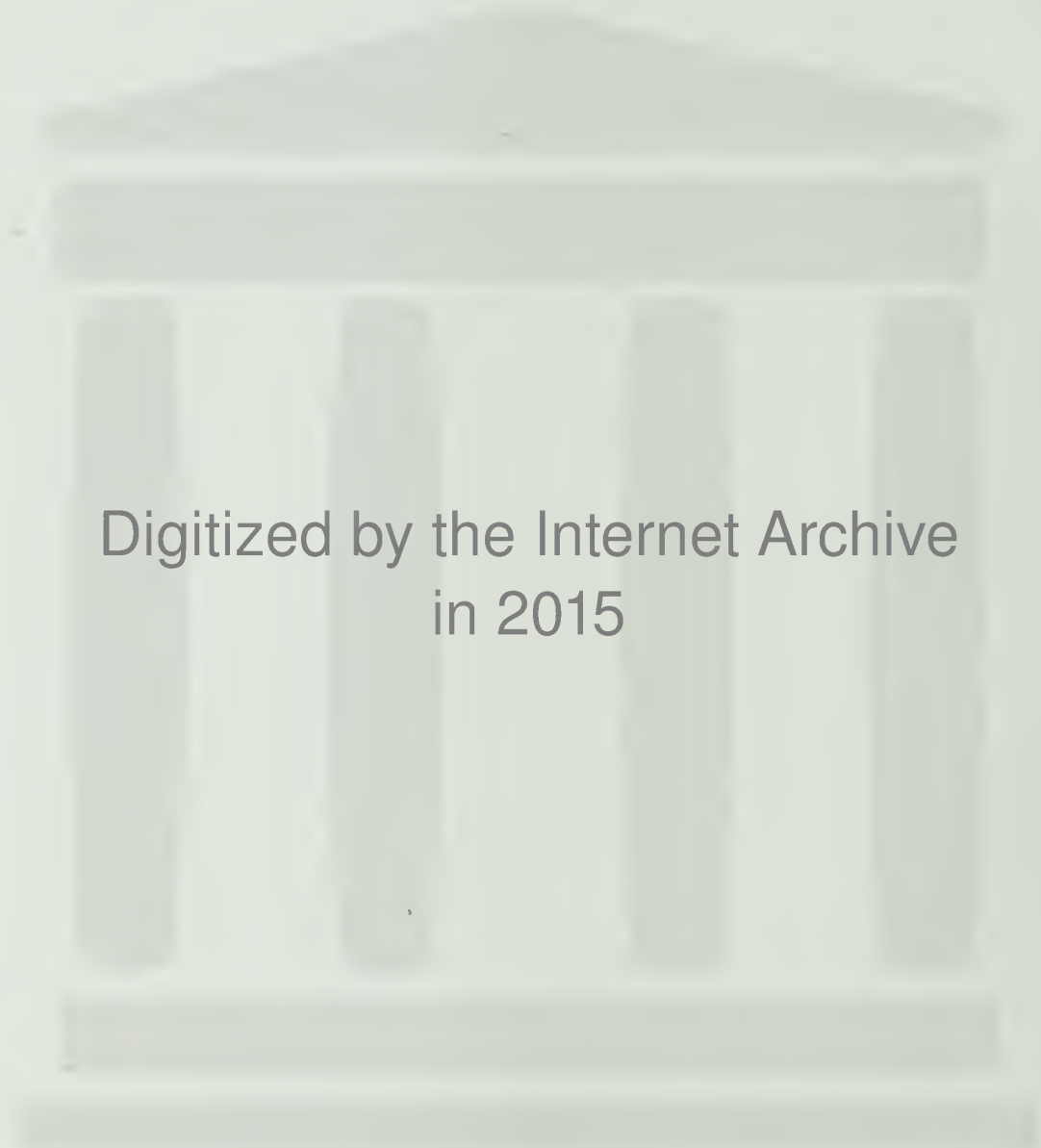
No. 16. The specificity of anti-venomous sera with special reference to a serum prepared with the venom of the Daboia Russellii, by *Captain G. Lamb, I.M.S.* Price As. 6 or 7*d.*

No. 17. Snake-venoms in relation to Hæmolysis, by *Captain G. Lamb, I.M.S.* Price As. 6 or 7*d.*

No. 18. Hæmogregarina Gerbilli, by *Lieutenant S. R. Christophers, M.B., I.M.S.* Price As. 10 or 1*s.*

No. 19. On Kala Azar, Malaria and Malarial Cachexia, by *Captain S. P. James, M.B., I.M.S.* Price Re. 1-4 or 1*s.* 11*d.*

Published by and on sale at the Office of the Superintendent of Government Printing, India, Calcutta. Copies are also available from all Agents for the sale of Government publications.



SERUM-THERAPY OF PLAGUE IN INDIA.

INTRODUCTION.

THE papers published in this number relate to trials in the Bombay Municipal Plague Hospitals, of the sera prepared according to the me thods of Professor Lustig of Florence, Professor Terni, formerly of Messina, now of Milan, Dr. Brazil of San Paulo, Brazil, and Dr. Roux of the Pasteur Institute of Paris.

Originally they were submitted to Government in the form of letters reporting results as the experiments progressed, and the work of the editor has simply been to produce connected reports from the materials submitted to him for this purpose. Though it has been necessary therefore to recast the reports, the sense and, as far as possible, the original wording, have been retained.

The first to try anti-plague serum in India was Yersin, who reached Bombay early in 1897, bringing with him serum prepared in Tongkin and at the Pasteur Institute at Paris. Its mode of preparation is thus described by Roux [1]. "The anti-plague serum from horses 21 and 31 was prepared in the following way:— The horses first received dead cultures of plague bacilli subcutaneously; afterwards they received dead cultures by intravenous i njection. Lastly they received living cultures by intravenous injection."

Yersin treated a considerable number of private patients in Bombay, the results being communicated by him to the Plague Committee as follows :—

		Died.	Recovered.	Percentage mortality.
Treated on first day of illness	17	2	15	12
„ second „ „	17	6	11	35
„ third „ „	12	6	6	50
„ fourth „ „	3	2	1	66
„ fifth „ „	1	1	0	100
TOTAL TREATED	50	17	33	34

He further said that "the serum used in these experiments was supplied by the Pasteur Institute of Nha trang. It had to be prepared in great haste,

so it was weaker than that used last year in China, and the doses to be injected consequently had to be largely increased."[2]

The following summarises those cases treated either by himself or under his directions by other medical men, in the Bombay hospitals.

In the Parel Old Government House Hospital 27 persons were inoculated with Yersin's serum; the first three being injected by Yersin himself and the rest by Captain Thomson, I.M.S.

Three of these must be excluded as the patients were not suffering from plague, but from (*a*) meningitis with osseous tumour pressing on the medulla, (*b*) hepatitis and remittent fever, (*c*) some other disease not specified. One healthy woman was given a prophylactic injection, and must also be excluded. Of the remaining 23 individuals who undoubtedly had plague, 14 died and 9 recovered, giving a percentage mortality of 60·86.[3] The general mortality in the Parel Hospital at the time was 64·5, but as the Medical Officer in charge points out, there were among them a large number of moribund cases, which more than accounts for the difference.

Captain G. S. Thomson, M.B., I.M.S., who was in charge of the cases, reports that "the temperature, pulse and respirations were recorded and taken personally immediately before injection in each case." He notes the following as results following the injection of the serum:—Fall of temperature in many cases, fewer complications, lessening of the delirium. "No improvement in the general condition of the patients could be seen, and the inflamed glands were certainly not favourably affected." Convalescence did not seem to be quicker than in cases under the ordinary treatment.

In other hospitals in Bombay nine more patients were treated by Yersin. Of these one, who recovered, may be omitted as having been already inoculated with Haffkine's plague prophylactic, which as is well known favourably influences the course of the disease in those contracting plague subsequent to inoculation. Of the eight patients, five died and three recovered.

The table below shows at a glance the results in these three classes of patients:—

	Number.	Deaths.	Recoveries.	Percentage mortality.
Cases treated in private houses .	50	17	33	34·0
" " " Parel Hospital .	23	14	9	60·86
" " " Charni Road and Sahib's Servants Hospital .	8	5	3	62·5
TOTAL .	81	36	45	44·4

It will be noticed that the case mortality in hospital is almost the same as that recorded for the same class of patients in Dr. West's report on the trials with Roux's serum last year (*vide* p. 60).

Further trial of serum made on this system was carried out about the same time by the German Plague Commission on 26 patients in the Bombay Plague Hospitals. Of these 13 died and 13 recovered[4]; but as noted by the Indian Plague Commission, these results are not compared with any parallel series of controls, and are not therefore of much statistical value, though the case mortality is below the average met with in plague.

The serum used for these cases is described by the German Commission as belonging to " the older " sample supplied to them, and they record that " the only certain inference which can be drawn is that the injections of serum have had no perceptible immediate or remote harmful results."

The next trial with Roux-Yersin serum was made by Captain H. D. Mason, M.R.C.S., R.A.M.C., in the State of Cutch, during May and June 1897. The serum was obtained direct from the Pasteur Institute in Paris. " The serum was administered to human plague patients in doses from 10 to 60 c.c. The smaller doses were employed in the cases first treated, the larger doses being resorted to as experience was gained. Quantities larger than 60 c.c. were not administered, because it was found that with this last dose the patients began to suffer from painful swelling of the joints.[5]"

The amount given varied from 10 c.c. (in one case) to 220 c.c. The following table shows the numbers who received (*a*) less than 100 c c. of serum, (*b*) those who received 100 c.c. and above, and (*c*) those who received 200 c.c. or above, with the case mortality in each :—

	Number.	Deaths.	Percentage mortality.
Patients receiving less than 100 c.c. .	28	13	46·4
,, ,, 100 c.c. and above .	66	41	62·1
,, ,, 200 c.c. and above .	6	5	83·3
TOTAL .	100	59	59·0
Control cases .	100	83	83·0

Unfortunately it is not possible to compare the case-mortality of these serum-treated patients with a parallel set of control cases, for " The plague cases that served as controls were admitted to the Brahmapuri Hospital at Cutch Mandvi during the period of eight days (from the 25th of May to the 2nd of June 1897) at the height of the epidemic, when the fatality of the disease was extreme as is

evidenced by the mortality of 83 per cent. in the hospital. The plague patients, however, who were treated with serum, were, with the exception of the first 5 cases treated, admitted to hospital during a period of four months of a declining epidemic, when we may presume the type of the disease to have been much milder. Again, only 31 of the 100 serum cases were admitted into the Brahmapuri Hospital, this apparently being in consequence of the decline of the epidemic in Cutch Mandvi. The remaining 69 cases were admitted into hospital in smaller places in the neighbourhood of Cutch Mandvi. The serum cases were thus hardly comparable with the control cases. It is indeed recognised by Captain Mason that the average severity of the disease in the control was greater than that in the serum cases.[6]" A comparison of the serum cases treated in the Brahmapuri Hospital from the 30th of May to the 9th of June 1897, *i.e.*, within a week after the date of admission of the last control case shows the following result :—

	Number.	Deaths.	Percentage mortality.
Serum-treated patients	19	14	73·7
Control ,, ...	001	83	83·0

As the Indian Plague Commissioners remark, " In view of the more favourable results arrived at by these last comparisons, it is obviously possible that the diminished mortality of the serum cases which is exhibited by the first table may be referable quite as much to the decline in the virulence of the epidemic as to an effect exerted by the serum treatment."

The effect of the serum treatment on the clinical symptoms is said by Captain Mason to be, a reduction of temperature, with a calming effect on the patients and a general amelioration of their condition. In the graver cases, however, this fall of temperature and general improvement is transitory, " the symptoms again become serious and the disease appears to run its course as if the serum had not been given.[7] "

The serum treatment did not prevent the appearance of secondary buboes, nor had it any effect on cases of primary plague pneumonia.

The Indian Plague Commissioners[8] conclude by saying that the statistics " are inconclusive as to the value of the serum employed by him. At the same time, we are disposed to think that the favourable impression which was created on the mind of Captain Mason by his observation of the clinical effects of the serum treatment furnishes a presumption in favour of the utility of Yersin's serum."

The next observations with this serum were those of Dr. Simond of the Pasteur Institute, Paris, who came out to India and conducted the experiments personally.

At Karad in the Satara District, 32 persons were treated by him between the 5th and 24th September 1897, in the hospital there.[9] The doses varied from 10 c.c. (in one case) to 30 c.c.; and the largest total given to any one patient was 90 c.c. in 4 doses. The following table shows the numbers who received (*a*) less than 40 c.c. and (*b*) 40 c.c. and above :—

	Number.	Deaths.	Percentage mortality.
Patients receiving less than 40 c. c. . .	11	9	81·8
„ „ 40 c.c. and above . .	20	11	55·0
„ „ unknown quantity . .	1	1	...
TOTAL .	32	21	65·6

Among the patients who received 40 c.c. and above there were two non-fatal cases marked doubtful plague by Dr. Simond. If these be eliminated, we get a case-mortality of 61·1 instead of 55, which again closely approximates to the results got with Roux's latest serum. Unfortunately there is no information as to the case-mortality of a series of comparable control cases.

Dr. Simond's second trial was made by him at Karachi in May and June 1898. The records of 70 cases are available, 37 of which were fatal, a case-mortality of 52·8 per cent. The Indian Plague Commissioners state :[10] "The case-mortality of these patients is not compared by Dr. Simond with the case-mortality of any series of controls. When the fact is taken into consideration that a large number of pneumonic cases were included in the group, and that all convalescent patients were excluded, it would seem reasonable to conclude that the mortality was below the average of that usually met with in plague."

They also point out that the case-mortality in the Seth Vishandas Hospital, where most of the patients were treated, was, in the period before 9th May (when the serum treatment was begun) 70 per cent. among 288 cases ; that in the period from 9th May to 6th June (when the serum was being used) the case-mortality among 74 non-serum-treated cases was 74 per cent. and among 47 serum-treated cases 47 per cent., giving a gross mortality in the hospital at this time of 63 per cent. among 121 cases ; and that in the period after the serum treatment was stopped the case-mortality among 38 cases was 55 per cent.

From these figures they conclude that (*a*) the type of case admitted to hospital while the serum was being used, was gradually becoming less severe, as indicated by the progressively lessening case-mortality returned from the hospital; this corresponding to the rapid decline of the epidemic in the latter half of May and beginning of June 1898 in Karachi town; and (*b*) that possibly the cases in the non-treated group "included a large number of moribund or hopeless cases," for otherwise it is hard to explain the somewhat higher case-mortality as compared with the rate in the pre-serum period, and the disproportionate height as contrasted with the immediately succeeding period. It is thus impossible to form "a definite conclusion as to the effect exerted by the serum on the case-mortality."

It is unfortunately impossible to found anything on the figures showing that the serum was more effective when used in the first days of illness, for the reason that the patients universally declared they were recently affected, from fear of prosecution for concealment of cases.

As to the clinical effects of the serum, it appears that "in fatal cases the treatment had not the slightest permanent effect on the temperature."[11] In certain cases, however, the temperature fell two or three degrees, especially after the evening injection. In cases ending in recovery, the serum appeared to act in much the same way, and the temperature did not reach normal any sooner than under ordinary treatment. The pulse, however, often became less rapid, and the tongue clean and moist after an injection of serum, and general improvement in symptoms was seen in many cases, even when recovery did not eventually ensue. The serum had no effect on septicæmic or pneumonic cases, and hardly any on cases developing secondary pneumonia, nor did it prevent this latter complication. Convalescence was likewise not affected by the treatment, and four cases developed rheumatic articular pains.

The Indian Plague Commissioners made trial of samples of this serum, kindly placed at their disposal by the authorities of the Pasteur Institute in Paris. Patients were treated by Lieutenant Stewart Douglas, I.M.S., at Bangalore in December 1898 and January 1899.[12] The cases in the South Camp Hospital were treated with serum, those in the North Camp Hospital were observed as controls; both hospitals admitting a similar class of patients.

In all, 49 plague patients were treated, these being all the cases of undoubted plague admitted, save those manifestly convalescent or *in articulo mortis*. Of these, 31 died giving a case-mortality of 61·2 per cent. The serum was administered once a day, the quantity given to the first 28 cases varied from 10 c.c. to 20 c.c., and to the remaining 21 cases 40 c.c. on the first day, and generally 20 c.c. on each subsequent day. Seventeen patients received less than 40 c.c. of serum, and of these 10 died, a percentage case-mortality of 58·8; while 32

patients received 40 c.c. of serum or more and had 21 deaths, a percentage case-mortality of 65·6. With the exception of eight all were well marked bubonic cases.

For the purpose of comparison the Indian Plague Commissioners give the following table which shows the admission of plague patients to the North and South Camp hospitals during the period covered by the administration of serum :—

	Number.	Deaths.	Case-mortality per cent.
North Camp Hospital—no serum used . .	54	29	53·7
South Camp Hospital, where most of the cases were treated with serum	73	35	47·9

It will be seen that there is a difference of 5·8 per cent. in favour of the hospital where serum was largely used, but it is pointed out that no conclusion can be drawn from this as the figures are small, and the previous history of the two hospitals showed that the patients in the North Camp Hospital always had the highest case-mortality. Thus, before the serum treatment was begun, 365 cases in the North Camp Hospital showed a case-mortality of 75 per cent., while 686 in the South Camp Hospital had a case-mortality of 58 per cent., a much greater difference than the above. " It was not observed that any of the symptoms were markedly alleviated by the serum treatment, or that the life of the patients was prolonged. The serum treatment did not give any better results in the cases where it was inaugurated early than in the cases where it was inaugurated in the later stages of the disease."[13]

The plague epidemic in Bangalore having died out, the rest of the serum was used in the Modikhana Hospital, Bombay, where Dr. Turkhud, who was in charge, kindly arranged that every second patient should be placed at the disposal of the Plague Commission for serum treatment. The actual treatment and recording of results was undertaken by Captain Walton, M.B., F.R.C.S., I.M.S., and Lieutenant Stewart Douglas, I.M.S., while Drs. Wright and Ruffer, members of the Plague Commission, watched the results.

The amount of serum injected was usually 40 c.c. on admission, often followed by a second dose of 20 c.c. later in the day; and on subsequent days two doses of 20 c.c. each.

As regards the total amount of serum administered we find 13 patients received less than 100 c.c. and that all these died; 13 received 100 c.c. or more, of whom 9 died, a percentage case-mortality of 69·2; and two received more than 200 c.c., of whom one died and one recovered.

The following shows the general result :—

	Number.	Deaths.	Case-mortality, per cent.
Control group	28	24	85·71
Serum group	28	23	82·14

The control and serum groups were strictly comparable. All were bubonic cases, all were males between 10 and 60 years of age, and the patients admitted to hospital and treated in the early and late stage of the disease were represented in nearly equal proportions in both groups. "The serum cases admitted and treated early with serum do not show any diminished case-mortality as compared with the untreated cases admitted in the same stage," nor do those treated early compare favourably with those treated later in the course of the disease.[14]

As regards the effect of serum treatment on the clinical features of the disease as illustrated by these cases at Bangalore and Bombay, the Plague Commissioners observe [15] that the temperature frequently falls within three or four hours after injection of the serum, but that this fall is only of temporary duration; and that occasionally a rise of temperature follows its administration. No characteristic difference in the temperature curve can be discovered when a series of charts of treated and non-treated cases are compared.

The pulse is often also affected in a temporary manner, becoming stronger, fuller and slower. Occasionally the pulse was not affected in cases where a favourable effect was produced on the temperature.

The respiration rate follows the pulse rate very closely, a distinct temporary improvement often following the administration of serum.

"The serum appears to exert no effect whatever on the buboes," and "little or no influence on the supervention or course of the lung complications which are so commonly met with in plague."

The effect of the serum injection on delirium and other nervous symptoms was favourable in many cases, but by no means constant. Apparently convalescence in those who recovered was not affected in any way, nor was life appreciably prolonged in the fatal cases by the treatment.

The only other trial in India of serum made on this plan, besides the cases reported on by Dr. West, was one conducted by the Russian Plague Commission with serum prepared in the Imperial Institute of Preventive Medicine, St. Petersburg.

The patients treated were those admitted to the Parel Hospital, Bombay, during March and April 1897. Every alternate patient was treated with the serum, the treatment being withheld only when the diagnosis of plague was

uncertain or when the patient was actually on the point of death. The serum was given hypodermically: at first 20 c.c. daily in one dose; later, an additional 10 c.c. was given in the evening, and later still the morning dose was increased to 30 c.c.

These doses were finally increased to 40 c.c. in the morning and 20 c.c. at night. "More than half the cases were treated with the later doses."[16]

The following table shows the result:—

	Number.	Deaths.	Percentage mortality.
Patients receiving serum	50	40	80
,, not receiving serum	50	40	80

There is nothing to show that the serum was more effective when given early in the course of the disease.

Dr. Clemow, who was in charge of the hospital, could not satisfy himself that the serum had any effect on the temperature, or on the ordinary complications of the disease.[17]

"It is impossible, in view of the above," say the Indian Plague Commission,[16] "to arrive at any other conclusion with regard to the effect of the serum employed than that which was arrived at by Dr. Jassenski, of the Russian Plague Commission, who conducted the test of the serum, and which was concurred in by Captain Jennings and Dr. Clemow, namely, that the serum was an absolutely indifferent substance with no influence either for good or evil, on the course of acute plague."

Haffkine's Anti-plague Serum.

Shortly after plague was recognised in Bombay, Mr. Haffkine was deputed by the Government of India to investigate plague from the bacteriological point of view, and to devise, if possible, a prophylactic for that disease. In November 1896, that is some six weeks after his arrival in Bombay, he began the inoculation of some 20 horses with plague microbes with the object of obtaining an anti-plague serum from them. The material employed for immunising the animals was a culture of plague germs in broth, such as is used in the manufacture of the plague prophylactic.

The initial dose was 5 c.c. of such a culture some two weeks or so old. "These animals in the course of several months or a year, could be brought to such a state that they could be safely inoculated with a litre or a litre and a half instead of 5 c.c."[18]

The injections were in all cases hypodermic, and besides a large number of horses, cattle, sheep and goats were used. The goats all succumbed to a

chronic disease induced by the injections, associated with wasting and swelling of the joints, and their serum therefore was not used. Serum from the horses, cattle and sheep was used in a large number of cases at Poona in the autumn of 1897. Preliminary experiments on animals had proved its efficacy in small doses to protect against lethal injections of living plague germs.[19] It was first used on human beings in the Byculla Jail and Arthur Road hospital, Bombay, in the early part of the same year. On account of the small amount of serum then available no clear indication as to its usefulness, or otherwise, could at that time be obtained. The serum procured from the animals was therefore stored in hermetically sealed test tubes till a sufficient amount had accumulated for the purposes of a crucial test. In the autumn of 1897, when plague was on the increase in Poona, an opportunity presented itself of making a series of systematic observations on the plague patients admitted to the special hospital there.

Mr. Haffkine, accompanied by the present writer, accordingly visited the plague hospital every morning, and by the kindness of Captain J. L. T. Jones, M.B., I.M.S., in charge of the hospital, was enabled to treat with this serum every alternate patient admitted to the hospital during the three hours or so we remained there daily.

As most of the cases were admitted in the morning as the result of house-to-house visitation by the authorities, and as some 20 or 30 patients were admitted daily, it was possible to obtain in a fortnight a decided opinion on the usefulness of the serum. No selection was made except when two patients arrived simultaneously. In such a case that patient was chosen for injection who seemed to us to be in the more serious condition. In this way close on 200 cases of plague passed through our hands, half of which were treated with varying amounts of serum, often in very large amounts. No evidence from clinical observation was obtained of any effect attributable to the serum, and the case-mortality was, probably on account of the method of selection noted above, some 14 per cent. higher in those treated with serum than in the controls. A hint of beneficial action was obtained in the case of patients treated with the sheep serum; but none in the case of those injected with the cattle or horse serum prepared in this way.

No further experiments were therefore performed with this serum.

Lustig's Serum.

Professor Lustig of Florence, having by experiment on small animals arrived at the conclusion that a curative serum for plague could be prepared by the injection of horses with nucleo-albumen derived from masses of plague germs treated with certain chemicals, was sent to Bombay by the British Government

in June 1897 for the purpose of trying his serum on human beings. By this time the plague epidemic of the first year had run its course and only a few sporadic cases were available for this purpose. Dr. Choksy, the Medical Officer in charge of the Arthur Road Hospital, where it was first tried, reported that it was "the only serum which gave anything like satisfactory results as out of 7 cases treated with this serum 6 recovered, and at Lanowli 16 cases were treated and 12 recovered."[20] Professor Lustig reports[21] that in Bombay and Poona he treated 30 patients with 24 recoveries.

On the strength of these favourable results and the report of further experiments on animals in Florence, the Municipal Corporation of Bombay asked Professor Lustig to prepare serum for them in Florence and agreed to engage the services of Dr. (now Professor) G. Galeotti, Professor Lustig's Assistant, and to arrange for the manufacture of serum on the spot. Dr. Galeotti and his Assistant Dr. Polverini arrived in Bombay on the 11th of March 1898 bringing a supply of serum which had been made in Florence by Professor Lustig.

The cases treated with this Florence-made serum numbered 257, all under the care of Dr. Choksy at the Arthur Road Municipal Hospital, and admitted in the period from March to October 1898. The serum was given hypodermically in doses of from 10 to 30 c.c. night and morning. "The patients to whom the serum was therapeutically administered were to some extent selected, all moribund patients being excluded, except in March and part of April. The case-mortality of the selected patients who were submitted to the serum treatment was compared with the case-mortality in the remainder of the hospital patients, including, as this did, the moribund patients who were excluded from the serum group. The results as set forth by Dr. Choksy were as follows"[22]:—

	Cases.	Deaths.	Case-mortality, per cent.
Ordinary treatment	752	595	79·1
Serum ,, ...	257	145	56·4

The Indian Plague Commission then proceed to discuss whether these two groups of cases are strictly comparable as regards severity and the distribution of moribund and convalescent patients, and arrive at the conclusion[23] "that when the desire to test the serum only on cases that seemed capable of benefiting from the treatment, and in particular upon patients who seemed likely to live more than 24 hours after admission, came to be a factor in the selection of cases for serum treatment, an influence was introduced, which must, no doubt

unconsciously, have operated in the direction of including within the serum group the milder, to the exclusion of the severer, cases of plague." They therefore believe that these statistics " do not afford any conclusive evidence of the efficacy of Lustig's serum."

The Bombay Municipal Corporation having resolved to start the manufacture of Lustig's serum on the spot, work was begun with five horses on the 1st of November 1898. Drs. Galeotti and Polverini were in charge of the laboratory and Professor Lustig himself came to Bombay in January 1899 to see its working and found it " completely satisfactory in every regard." Later in the year Dr. Galeotti had to return to Italy, when Dr. Polverini, his assistant, assumed charge and with the assistance of Dr. A. Mayr was responsible for the production of the serum till the close of the Municipal Laboratory in June 1902. Dr. A. Mayr has kindly written out a clear statement of the methods used by them in the immunisation of the horses (*vide* Appendix A), which is most valuable as giving the results of the experience accumulated in this matter.

The first trial of Lustig's serum as locally manufactured in Bombay was made in the period from February to April 1899, and relates to 403 serum-treated patients admitted to the Arthur Road Hospital under the care of Dr. Choksy.

" In this series of observations only patients admitted in the acute stages of the disease and in a non-moribund condition were treated with the serum. The residuum of patients admitted to the hospital during the corresponding period was, as in the series of observations that have just been considered, taken as control."[24] The result was as follows:—

	Cases.	Deaths.	Case-mortality, per cent.
Control group	1,190	957	80·42
Serum „	403	249	61·73

It has been contended that the method of selection was a fair one, not tending to the taking of a milder type of case for serum treatment; and that therefore comparison with the control group is permissible. But on the other hand the Indian Plague Commission point out that the exclusion of moribund patients from the serum group is in fact substituting a set of patients with a case-mortality of between 64 and 65 per cent. for one with a case-mortality of 100 per cent., and therefore to that extent lowering their death rate. Secondly, they remark that it is not correct to compare the case-mortality of the Modikhana and Maratha plague hospitals where serum was not used, with the control cases of the Arthur Road Hospital, because, as only 25 per cent. of the total patients

admitted to the latter institution were chosen for serum treatment, an opportunity was not afforded for an appreciable increase in case-mortality in the large number of cases not so treated. They, therefore, conclude that this second series of observations cannot be regarded as affording conclusive evidence of an advantage accruing from serum treatment.

The third series of observations made at the Arthur Road Hospital is dealt with at length by Mr. Haffkine in his report (*vide* p. 28) and need not therefore be referred to here.

In the other hospitals in Bombay, Lustig's serum was used as follows [25] :—

MARATHA HOSPITAL.	Serum Treatment.			Ordinary Treatment.			Difference in favour of serum group, per cent.
	No.	Deaths.	Case-mortality, per cent.	No.	Deaths.	Case mortality, per cent.	
1898, selection . . .	28	17	60·71	..	...	80 7	20·0
Nov. 1900 to Jan. 1901, selection	38	32	84·21	...	...	88 8	4·59
August to December 1901, ,,	44	31	70·45	203	161	79·31	8 86
April and May 1902, alternate .	31	31	100·0	31	29	93·54	*Nil.*

In the first three sets of cases noted in the above table a process of selection was in force, which, however impartially applied, always precludes the possibility of arriving at a perfectly definite conclusion. The fourth set of cases, marked alternate, were under the supervision of Dr. A. Mayr, and formed a series treated in serial succession with Lustig's and Roux's serum and ordinary symptomatic treatment. With regard to these cases, Dr. Choksy remarks : [26] "The 31 cases under Lustig serum included 16 septicæmic cases, 2 were received dead in their turn, and 3 non-septicæmic cases who were not injected because they were moribund. Thus 21 cases became excluded as incurable and there remained only 10 cases fit for treatment, all of whom died. Of the 31 Roux's serum cases 15 were septicæmic, 1 was received dead, and 2 non-septicæmic cases were not injected because they were moribund. Thus 18 cases were excluded, and of the 13 who remained, 2 recovered. There were 13 septicæmic cases among those under ordinary English treatment, and no cases were received dead. Of the 18 thus remaining 2 recovered—one a semi-convalescent case and another a mild case." He further notes that life was prolonged noticeably in the serum treated cases.

In the Parel Old Government House Hospital in 1898 with Dr. Clemow in charge, 13 cases "not selected in any way" were treated. "Every alternate case of plague admitted to the wards, provided the diagnosis was certain and

the patient not absolutely moribund, was submitted to the injections."[27] Of these 10 died, which is equivalent to a case-mortality of 77 per cent. These cases were injected by Drs. Galeotti and Polverini with Florence-made serum.

In the Modikhana Hospital in 1900 a fairly extensive trial of Lustig serum as made in Bombay was carried out by Dr. D. A. Turkhud, M.B. (Edin.), in charge of that plague hospital. The method of selection was as follows:—

All acute cases of plague, about the diagnosis of which there could be no doubt whatever, were taken for the trial, and each alternate case in the order of admission into the ward, was taken for serum treatment. The following classes of cases were not used either as controls or for serum treatment: (*a*) Convalescent plague cases; (*b*) Cases admitted into the observation ward as being at that time not recognisable as certainly plague cases.

In these two categories 43 cases are included and it has been contended [28] that in excluding patients who on admission were "doubtful cases" of plague, an unwarrantable interference with the alternate system was brought about. But, as pointed out by Dr. Turkhud, had these cases been taken for serum treatment when the diagnosis was arrived at after a day or so in hospital, it might have been said that they were put under treatment too late, and anyhow as the cases were left out of account altogether it does not appear why this procedure should favour one side more than the other. The following shows the result:—

MODIKHANA HOSPITAL. 26TH JANUARY TO 27TH FEBBUARY 1900.	Cases.	Deaths.	Case-mortality, per cent.
Serum patients	66	54	81·81
Control ,, ...	66	48	72·72
Observation ward patients . . .	43	32	74·41

Excluding 30 cases dying within 30 hours of admission, the doses administered varied from 20 c.c. (in one case) to 160 c.c.; the average working out at 49·4 c.c. for each case. Eleven cases received 100 c.c. or above.

In view of the unfavourable results obtained in this hospital, the following criticism was made by Dr. Polverini,[29] *viz.*:—(*a*) That the alternate system was not strictly observed. (*b*) That the serum was not given regularly or at proper hours. (*c*) That the doses were insufficient. (*d*) That the total quantity said to have been used was in excess of that supplied to the hospital. The first heading has already been dealt with. As to (*b*) and (*c*) Dr. Turkhud says, [30] "It is true that I was never, owing to other work, able to give the morning

injections before 8 o'clock," but otherwise the serum was administered regularly, and in accordance with the instructions given by Dr. Polverini at the time as regards dosage and method of injection. As to (*d*) it appears some error must have been made in the laboratory, for the amount used in the Modikhana Hospital corresponds to the amount noted by Dr. Polverini in his own letters as having been sent.

The only other cases treated with Lustig's serum in the Bombay hospitals were eight in the Parsi fever hospital in 1899-1900, of which five died and three recovered; and two selected cases treated in the Modikhana Hospital in 1901, of which one died.

Yet one other attempt was made to treat patients with Lustig's serum on the alternate plan. The operations were under the direct supervision of Major W. E. Jennings, M.D. (Edin.), D.P.H., I.M.S., and carried out by Dr. C. T. Costello at the Poona Plague Hospital. The experiment was begun on the 4th of February 1902 and continued for a month, during which time 60 patients were admitted to the hospital. Of these, five were not taken for the experiment for the following reasons: three were "practically dead" (two of whom should have been taken for serum treatment, and one for the ordinary treatment); one was a patient almost quite recovered who was transferred from another plague hospital on its closure; one was the son of a ward servant living on the premises about whose illness there was some doubt and who, moreover, had suffered from plague two years previously.

The exclusion of these cases in no way vitiated the test, as they were regarded for this purpose as non-existent, and the next admission taken for serum or ordinary treatment as the case might be. The fate of the remaining 55 patients is shown in the following table:—

	Cases.	Deaths.	Case-mortality, per cent.
Serum cases	27	21	77·7
Control „	28	20	71·4

The serum was given hypodermically and the amounts varied from 40 c.c. to 1210 c.c.; the average administered being 348·5 c.c. Four patients received less than 100 c.c.; nine received between 100 and 200 c.c.; two received between 200 and 300 c.c.; two received between 300 and 400 c.c. and 10 received 400 c.c. and above. The patients in the serum group received also the ordinary symptomatic treatment.

A capsule of blood was taken from each patient on admission, and sent to the Plague Research Laboratory, Bombay, where it was examined by culture and injection into animals. The results are shown below :—

	Plague bacilli		Percentage of cases in which found.	No examination as the capsule was broken when received.
	Found in	Not found in		
Serum cases, 27 . .	7	19	25·9	1
Control cases, 28 .	12	13	42·8	3

It will be noticed that the control patients showed a much larger number of septicæmic cases on admission than the serum group of cases. It is certain therefore that if there was any difference in the gravity of the cases in the two groups of patients, the control group had the larger number likely to have a fatal ending; for Captain E. D. W. Greig, M.B., B.Sc., I.M.S., proved, about this time, from the examination of 132 plague cases in Bombay, that the case-mortality of septicæmic cases is extremely high (97·6 per cent.) while those in which bacilli are not present in the blood at an early period of the disease, have a case-mortality less than half of this (44·1 per cent.).[31]

The serum treatment appeared to have had no effect on the symptoms.

The average duration of illness was longer in the serum cases by 30 hours; but this is largely accounted for by the chance that one serum case survived for 18 and another for 8 days. It is always difficult in small groups of cases to apportion correctly cause and effect.

Cases in Private Practice.

In Dr. Choksy's papers on the "Treatment of Plague with Professor Lustig's Serum,"[32] there is published an account of 130 cases of plague treated by himself and other medical men in their private practice.

The following shows the results :—

	Cases.	Deaths.	Case-mortality, per cent.
Dr. Choksy's cases	74	40	54·05
Cases in others' practice . . .	56	18	32·14
Total cases treated .	130	58	44·61

The difference in these two sets of figures may be accounted for on the supposition that Dr. Choksy being rightly regarded as an expert in plague, was called in consultation to see cases where the treatment of others had failed.

As regards the effects of early treatment on these private patients, Dr. Choksy remarks:—"Of the 26 patients treated on the first day of illness, 4 succumbed and 22 recovered, whereas, of the 34 treated on the second day, 20 died and 14 recovered. The mortality rate in the former case being equivalent to 15·38 per cent. only, as against 58·82 among the latter. And this clearly indicates what a few hours delay would mean in the treatment of such a rapidly fatal infection as that of plague."

The clinical effects noted by Dr. Choksy in these cases are much the same as those already described by Mason, Simond and others (*vide supra*), *viz.*: rising temperature was arrested in its upward course, and fell more rapidly than usual; buboes became hard and painless, and subsided without suppuration. The general condition was improved, the mind became clearer, "hardly any nervous prostration or enfeeblement of the circulation could be noticed; sleep became natural and the patient was generally cheerful, scarcely realising that he was afflicted with such a grave infection as plague." These remarks, however, apply only to cases treated on the first day of the illness, those injected on and after the second day did not show the same amelioration of symptoms, "the course of the disease was not always shortened and suppuration of the buboes was the rule."

Terni's Serum.

Early in 1901 two small samples of this serum were received from the Secretary of State for India, and from Messina direct. As only a small amount of serum was received, Mr. Haffkine suggested that it should be tried on a few "serious plague cases."

This was accordingly done at the Maratha hospital on 8th February 1901, the patients being chosen by Mr. Haffkine and a Committee of three medical men.

The first patient was a man aged 25, in the fourth day of the disease, with temperature ranging from 102·8° to 103·2° F., pulse 108, feeble, respirations 24 per minute. Bubo in left groin, painful and œdematous. Plague bacilli were present in the bubo, not in the blood. He got at once 61¾ c.c. of serum hypodermically, but this had no effect on temperature, pulse and respiration. In the afternoon of the same day he got 38 c.c. more of serum. Next day he was quiet and collapsed, with slight cough due to commencing pneumonia. He died on the 10th February, the serum having apparently had no effect whatever.

The second patient was a male, aged 35, admitted to hospital on the 11th February 1901 in the second day of illness and treated on the 12th idem. The patient was a strong man, quite sensible, and a markedly milder case than the former one. Temperature ranged between 101·2° and 102·8° F., pulse 132 fairly strong, respiration 25 per minute. Bubo in left femoral region, painful and œdematous. Plague bacilli were present in the blood as well as in the bubo.

He was given 59 c.c. of serum. Four hours afterwards he had a severe rigor of short duration, during which the temperature fell to 97·8° F. The temperature shortly after rose to 103° F. At 5 P.M. on the same day 60 c.c. of serum was injected, but the man died 1½ hours after.

The history of the only other cases treated with this serum is given in detail by Mr. Haffkine and Dr. Costello in the body of this report (*vide* p. 37), so it is necessary here to give information only as to its manufacture.

In a summary describing his methods forwarded with a letter, dated from the Institutio d' Igiene, Messina, 27th October 1901, Dr. Terni says that having found the benefit of using virulent cultures when preparing a vaccine for plague, he "proposed to produce the vaccinating material directly in the bodies of animals (guinea-pigs and monkeys) by injecting cultures in glycerinated bouillon (3 per cent.) into the peritoneal cavity. In this manner an abundant exudation is obtained, which is very rich in bacilli, and in toxic and anti-toxic substances produced in the lymphatic cavity, similar to those obtained from a plague bubo. The material is rubbed up with a sterile solution of 0·75 per cent. sodium chloride, and 1 per cent. of sodium carbonate to prevent coagulation. It is then exposed to fractional sterilization at 55 to 58° C. and then 0·5 per cent. of carbolic acid is added. The exudation which is obtained is thready, almost gummy, very different from the pus produced by pyogenic or other microbes of infection; and this characteristic suffices to indicate that no other germs have penetrated, even before the bacteriological examination necessary to guarantee the purity of the material."

With this material used as a vaccine Dr. Terni reports good results from Rio-de-Janeiro, and he used it accordingly to immunise the animals destined to furnish his curative serum. He says: "As to the serum, having proved that horse serum is absolutely ineffective, because it does not destroy the toxines and proteines of the plague bacillus, or only in very small proportions; and that injection produces in the blood scarcely any of those anti-bacterial and antitoxic substances which are useful as curatives; and after many attempts to produce a more active serum with animals of different species, I have used by preference mules and cattle. These were injected intravenously with the peritoneal exudation produced as for the preparation of the vaccine. The material is collected, rubbed up with sodium chloride and sodium carbonate, filtered through a sterile

metal sieve with a mesh of 0·1 m.m., or through a piece of sterilised cloth. It is inoculated intravenously in increasing quantities, beginning with 5 c.c., and the animals then give a serum of exceptional curative value."

Brazil's Serum.

A trial consignment of this serum was received through the Secretary of State for India towards the end of 1902. The consignment consisted of 36 sealed test tubes of serum, but unfortunately only 8 were found fit for use on opening the boxes.

Under Mr. Haffkine's directions two cases were chosen "of a typically severe type, in order to avoid such as might recover under treatment without serum." One received hypodermically 66 c.c. of serum, the other 110 c.c. Both died, and no evidence was found either clinically or otherwise of benefit attributable to the serum treatment. Both were treated in the Modikhana Hospital, under the observation of Dr. Costello.

In August 1903 another consignment of 600 tubes was received with which the trial reported on by Mr. Haffkine and Dr. West was made. (*Vide* p.47.)

The mode of preparation of this serum is thus described by Dr. Vital Brazil, Director of the State Serum Institute, San Paulo, Brazil[33] :—

"The immunisation of the animals began in the middle of November 1899 soon after the appearance of the plague in the port of Santos. The animals were prepared in the following way :—(1) by the injection of cultures killed by heating to 60° C., the doses being gradually increased; and (2) by the injection of living cultures in doses gradually increasing in amount and virulence.

Experimentally the serum showed both preventative and curative action, the animals experimented on being guinea-pigs, rats and rabbits. A dose of 0·5 of a cubic centimetre of serum was found sufficient to protect a guinea pig weighing 500 grammes against an injection of virus which produced the death of an unprotected guinea-pig in four days."

SUMMARY.

The trials of curative serum above described, and those more elaborately dealt with in the subsequent part of this report relate to all the cases treated in India up to May 1904, as far as they are known to the writer.

They may be conveniently divided into two categories :—

(*a*) Those in which the conditions of trial were reasonably accurate, and where a series of control patients strictly comparable with those treated with serum was available ; and

(*b*) Those in which though the records of the serum treated cases may be accurate, yet the control patients, where such are reported,

were not in all respects strictly comparable for one reason or another with those receiving the serum treatment.

The tables I and II below show at a glance the results obtained in each case.

TABLE I.—Conditions as in (a)

	SERUM CASES.				CONTROL CASES.			
	No.	Deaths.	Recoveries.	Case-mortality, per cent.	No.	Deaths.	Recoveries.	Case-mortality, per cent.
Roux Yersin serum by Indian Plague Commission (Bangalore).	49	31	18	63·26	54	29	25	53·7*
Roux Yersin serum by Indian Plague Commission (Bombay).	28	23	5	82·14	28	24	4	85·7
Roux Yersin serum by Russian Commission (Parel).	50	40	10	80·0	50	40	10	80·0
Roux Yersin serum by Dr. Mayr (1902).	31	29	2	93·54	31	29	2	93·54
Roux Yersin serum by Dr. West (Bombay).	68	45	23	66·17	68	41	27	60·29
TOTAL TREATED WITH ROUX YERSIN SERUM.	226	168	58	74·33	231	163	68	70·56
Lustig's serum (Dr. Turkhud, 1900).	66	54	12	81·81	66	48	18	72·72
Lustig's serum (Dr. Mayr, 1902)	31	31	...	100·0†	31	29	2	93·54
Lustig's serum (Poona, 1902).	27	21	6	77·7	28	20	8	71·42
Lustig's serum, 3rd series (Bombay).	484	330	154	68·18	484	385	99	79·54
TOTAL TREATED WITH LUSTIG'S SERUM.	608	436	172	71·71	609	482	127	79·14
TERNI'S SERUM . . .	110	89	21	80·90	110	90	20	81·81
Brazil's serum (Maratha hospital).	50	41	9	82·0	50	45	5	90·0
Brazil's serum (Modikhana hospital).	20	17	3	85·0	20	15	5	75·0
TOTAL TREATED WITH BRAZIL'S SERUM.	70	58	12	82·85	70	60	10	85·71

* But *vide p.7 supra*, for details of comparison.

† *Vide* Dr. Choksy's remarks, p. 13, *supra*.

TABLE II.—Conditions as in (b).

	Serum Cases.				Contrasting Cases.			
	No.	Deaths.	Recoveries.	Case-mortality, per cent.	No.	Deaths.	Recoveries.	Case-mortality, per cent.
Cases treated by Yersin in private.	50	17	33	34·0	No contrasting cases.			
Yersin's serum in Parel Hospital.	23	14	9	60·86	General Hospital Mortality.			64·5
Yersin's serum in Charni Road and Sahib's servants hospitals.	8	5	3	62·5	86	62	24	72·1*
Roux Yersin serum by German Commission.	26	13	13	50·0	No contrasting cases.			
Roux Yersin serum by Captain Mason.	100	59	41	59·0	100	83	17	83·0†
Roux Yersin serum by Dr. Simond (Karad).	32	21	11	65·6	No contrasting cases.			
Roux Yersin serum by Dr. Simond (Karachi).	70	37	33	52·8	74	55	19	74‡
TOTAL TREATED WITH ROUX YERSIN SERUM.	309	166	143	53·7	260	200	60	76·9
Cases treated by Professor Lustig (Bombay and Poona).	30	6	24	20·0	No contrasting cases.			
Lustig's serum, by Dr. Clemow (1898).	13	10	3	77·0	No contrasting cases.			
Lustig's serum, first series (Bombay).	257	145	112	56·4	752	595	157	79·1§
Lustig's serum, second series (Bombay).	403	249	154	61·78	1,190	957	233	80·42‖
Lustig's serum, Maratha hospital, 1898 and 1900-01.	66	49	17	74·2¶	General Hospital mortality			80·7 & 88·8
Lustig's serum, Maratha Hospital, 1901.	44	31	13	70·45¶	203	161	42	79·31
Lustig's serum in private practice.	130	58	72	44·61	No contrasting cases.			
TOTAL TREATED WITH LUSTIG'S SERUM.	943	548	395	58·1	2,145	1,713	432	79·8
TERNI'S SERUM (1901) . .	2	2	...	100·0	No contrasting cases.			
BRAZIL'S SERUM (1902) . .	2	2	...	100·0	No contrasting cases.			

* Total mortality in this hospital.
† But *vide* p. 3 *supra* for details.
‡ But *vide* p. 5 *supra* for details.
§ But *vide* p. 11 *supra* for details.
‖ But *vide* p. 12 *supra* for details.
¶ Selection method.

From a study of these tables it is evident that we have to deal with a remedy much less effective than serum proves itself to be in the case of diphtheria. This was recognised early in these trials, and it became necessary

therefore to study a large series of cases treated by ordinary methods and by serum side by side, in a strictly scientific manner, before a conclusion could be arrived at. This has, I think, been to a large extent secured in the case of the trials enumerated in Table I, and it is by a consideration of these alone, that a true estimate of the worth of serum treatment for plague as at present practised can be reached.

To take first the case of the Roux Yersin serum, it is seen that in all the trials, save one, the case-mortality of those treated with serum is as high or higher than that of the control patients. The one exception is in the series of 28 cases treated in Bombay by the Indian Plague Commission, in which one patient fewer on the serum side died than among the controls. The element of chance must be reckoned with here, as the numbers are small.

With regard to the trial of the serum sent personally by Dr. Roux and dealt with fully in Dr. West's report, it is a matter for regret that permission to employ the intravenous method was not obtained at an earlier stage of the experiment, so that a greater number of patients might have been thus treated. Dr. Roux maintains that subcutaneous injection, entailing as it does slow absorption of the serum into the circulation, gives time for the formation in the patient of anti-bodies to the serum anti-toxin so that the plague bacilli in the blood are not affected by the serum. They may even, as Ainley Walker[34] has pointed out, become accustomed to the presence of the anti-toxin and thereby have their virulence increased. Roux maintains that the full dose of serum should be injected straight into the blood stream, so that the bacilli may be overwhelmed at once, by mass-action as it were.

If the patients dealt with in this trial be divided into three groups, according as they were treated :—

(*a*) by subcutaneous injection only ;

(*b*) by subcutaneous injection to begin with, followed by intravenous injection ; and

(*c*) by primary intravenous injection, followed by similar injections, or in some few cases by subcutaneous medication ;

the following table can be constructed :—

	Serum Cases.			Control Cases.		
	No.	Deaths.	Case-mortality, per cent.	No.	Deaths.	Case-mortality, per cent.
Patients treated according to (*a*) . . .	43	29	67·4	43	28	65·1
Patients treated according to (*b*) . . .	12	8	66·6	12	6	50·0
Patients treated according to (*c*) . . .	13	8	61·5	13	7	53·8
Total .	68	45	66·2	68	41	60·3

From a study of the case-mortality of the control cases corresponding to those treated with serum as above divided, it is evident that the epidemic was declining in severity as time went on. It is not therefore possible to say that the lessened case-mortality shown by the 13 cases treated according to (*c*) is due to that treatment, for a corresponding and even greater lessening of the case-mortality is exhibited by the 13 alternate control cases receiving the ordinary treatment.

We must, therefore, reluctantly conclude that the serum treatment, as judged by these figures, did not affect the case-mortality in the slightest degree.

In three out of the four trials made with Lustig's serum we find that the case-mortality of the serum-treated patients is higher than among those receiving ordinary treatment.

The exceptional case is that treated at length in the report forming the first of those published in this memoir. From Table II of this report we learn that of the category showing the lowest mortality (*i.e.*, those in whom both pulse and respiration were slow) the serum group of patients had 46, while the control group comprises only 24 such cases.

Table III of the same report shows that cases without buboes were "practically all fatal." Of these the controls had 29, while the serum-treated cases had only 5. Table V shows that the sex distribution likewise is in favour of the serum cases.

From a consideration of these tables and the details set forth in Mr. Haffkine's report we must reluctantly arrive at the conclusion, that, judged by these figures alone, there is no certain evidence that the serum is efficient.

The trial made with Terni's serum shows the difference in favour of the injected patients to be 0·91 per cent. only, an amount which cannot be regarded as of the slightest significance.

As regards Brazil's serum it seems highly problematical if the 2·85 per cent. of the life-saving shown amongst the treated cases can be credited to the effects of the treatment. For in one hospital we find that of the serum-treated patients ten per cent. more died, while in the other, eight per cent. fewer of the cases had a fatal termination.

From the stand-point of clinical evidence, however, there is more hope in the outlook. Almost all the clinicians who have reported on the use of serum in their hospitals or in private practice are emphatic that it acts favourably on the course of the disease.

It seems, for instance, that the serum-treated cases live longer than the control cases.

The following statement brings this out :—

Kind of serum used.	Average number of days in hospital in fatal cases in		Advantage in favour of serum-treated cases.
	Serum Cases.	Control Cases.	
Roux	7·57	4·19	3·38
Lustig	3·89	2·76	1·13
Terni	3·27	2·93	0·34
Brazil { Maratha Hospital . . .	2·56	2·25	0·31
Brazil { Modikhana „ . . .	2·06	4·61	−2·55

It is a curious circumstance, as noted by Mr. Haffkine, that serum should have the effect of prolonging life, and yet be apparently powerless to affect the case-mortality of hospital cases. Perhaps the proper method of administration has not yet been arrived at; for undoubtedly in the case of animals artificially infected with plague the serum proves efficacious when given within a reasonable time after infection. It is therefore a matter for regret that more cases were not treated intravenously as suggested by Dr. Roux. Time is everything when treating such a virulent and rapidly fatal disease as plague, and it is well to remember the results obtained by Martin when working with snake venom. He found that the proportion of toxine to anti-toxine necessary for neutralisation was approximately the same whether they were allowed to act on one another in a test tube before injection, or were injected separately but simultaneously in different parts of the body, *provided the serum was given intravenously.* When however the serum was injected subcutaneously, at least twenty times the quantity was required to save the life of the animal. The reason for the failure of the anti-toxic serum used by Martin[35] when given subcutaneously, was its slow absorption into the system of the experimental animal, due to the large size of the molecular molecule of the anti-toxine. Starling[36] has shown that the walls of the capillaries are relatively impermeable to proteids, and Martin has proved that antivenene is a body " of great molecular size " compared with proteids. It is, therefore, reasonable to suppose that antivenene and other anti-toxines will also be very slowly taken up by the capillaries.

Other effects attributed to the serum by those who have used it are (*a*) lowering of the temperature, (*b*) lessening of rate of pulse and respiration, (*c*) a general improvement in the patient's condition as to physical comfort, and a diminution of delirium and restlessness, and (*d*) disappearance of the buboes and lessening of pain in them.

In such a virulent disease as plague is in India, these are no small gains, but it must be remembered that 60 per cent. of all bubonic cases are at the time of admission to hospital septicæmic. It has been urged by certain competent authorities (*e.g.*, Roux) that it is quite out of the question to expect to get any results with cases far advanced in the disease [37] and that therefore the alternate method hitherto tried in Indian hospitals is not one to bring out the true value of serum treatment.

But perhaps it would be possible to get an experienced clinician to select such cases as he deemed suitable for serum treatment and to admit them to a separate ward where they could be submitted to the alternate method of treatment by an independent observer.

When comparing the effects of the various sera as described in this memoir, it is necessary to remember that they differed much as regards freshness. Thus Lustig's serum being made locally was often used within a few days of separation from the blood; Brazil's serum had been kept for six months in the ice chest after receipt in India, and so on. Particulars as to date of receipt and use will be found in the detailed reports.

In view of the somewhat discouraging results obtained among hospital patients in India, it seems necessary to commence anew the study of the serum therapy of plague.

This, as suggested by the Indian Plague Commission, should be done by studying the action of plague toxines on animals and the blood changes taking place in men and animals injected with living plague or its toxines.

It would be necessary also to find out whether the insusceptible horse is the best manufacturer of plague curative serum. Brazil and Haffkine seem to have been the only experimenters with serum from animals other than the horse. Judged by the effect of serum on rabbits it appears [38] that the toxicity of serum from various species of animals may be arranged in the following order of decreasing virulence, *viz.*,—bullock, dog, calf, sheep, ass, and horse serum; but it does not follow that this order of toxicity would be maintained in the case of man.

W. B. BANNERMAN, M.D., B. SC.,
Lieutenant-Colonel, I.M.S.,
Director, Plague Research Laboratory.

REFERENCES TO INTRODUCTION.

[1] Report of the Indian Plague Commission, Vol. III, p. 382, Note 1. *Vide* also La Peste Bubonique, Par M. M. Yersin, Calmette et Borrel. Annales de l' Institut Pasteur, 1895, p. 591.

[2] Gatacre's Report, pp. 145-6. "Times of India" Press, Bombay, 1897.

[3] Report of the Indian Plague Commission, Vol. I, p. 395, also *vide* The Bombay Plague, Condon, 1900, p. 85, and General Gatacre's Report, 1897, pp. 78 and 80.

[4] Indian Plague Commission Report, Vol. V, p. 308.

[5] *Ibid*, Vol. V, p. 298, and Vol. III, p. 380.

[6] *Ibid*, Vol. V, p. 299.

[7] *Ibid*, Vol. V, p. 300.

[8] *Ibid*, Vol. V, p. 301.

[9] *Ibid*, Vol. III, p. 136 and V, p. 303.

[10] *Ibid*, Vol. V, p. 306.

[11] *Ibid*, Vol. V, p. 307.

[12] *Ibid*, Vol. III, pp. 593—643, and Vol. V, pp. 289—298.

[13] *Ibid*, Vol. V, p. 290.

[14] *Ibid*, Vol. V, p. 291.

[15] *Ibid*, Vol. V, p. 292.

[16] Jennings, Indian Plague Commission Report, Vol. V, p. 310.

[17] Clemow, Lancet, Vol. I, 1899, p. 1212.

[18] Mr. Haffkine's evidence; Indian Plague Commission Report, Vol. I, para. 115.

[19] *Ibid*, para. 135.

[20] Colonel J. Wilkins, I.M.S., in Report of Municipal Commissioner on the Plague in Bombay for the year ending 31st May 1899. Appendix E, p. 374.

[21] Memo. by Professor Lustig, to Health Officer, Bombay, *Ibid*. Appendix E, p. 376.

[22] Indian Plague Commission Report, Vol. V, p. 314.

[23] *Ibid*, p. 315.

[24] *Ibid*, p. 316.

[25] The Treatment of Plague with Prof. Lustig's Serum, page 110, by N. H. Choksy, M.D., Honoris causâ, Freiburg, Germany, Cor. Mem. Med. Soc. Munich, Special Assistant Health Officer, in charge of Arthur Road and Maratha Plague Hospitals, Bombay. "Eagle" Printing Office, Dalal Street, Fort, Bombay, 1903.

[26] Loc. cit., p. 111.

[27] The Serum Treatment of Plague; by Frank G. Clemow, M.D., Edin., D.P.H., Cantab. Lancet, May 6, 1899, p. 1215.

[28] Report on cases treated with Professor Lustig's Serum in 1899-1900, by Drs. Polverini and Mayr. Appendix IV, p. 378 of Report of the Municipal Commissioner on the Plague in Bombay for the year ending 31st May 1900. Bombay "Times of India" Press, 1901.

[29] Report of Municipal Commissioner for 1900, p. 378.

[30] In a letter to the writer.

[31] *Vide* Appendix B, Epitome of Greig's unpublished paper.

[32] *Vide* pages 113—115 of No. 25 of this list.

[33] Bombay Government Resolution, General Department (Plague), No. 2869-P., dated Bombay Castle, 30th October 1902. (Accompaniment.)

[34] Berliner Klinische Wochenschrift, 1901, Nos. 21 and 22.

[35] C. J. Martin, M.D., D.Sc., F.R.S., Director, Lister Institute. Proceedings, Royal Soc., 1898, Vol. LXIV, p. 88, and British Medical Journal, Vol. II, 1904, p. 901.

[36] Starling. Journal of Physiology, Vol. XIX, 1895-96, p. 311.

[37] Cf. Dr. Choksy. The treatment of Plague, p. 122.

[38] Serum Therapy, Bacterial Therapeutics and Vaccines, by R. T. Hewlett, M.D., p. 37. Note giving Salter's results. London, J. & A. Churchill, 1903.

REPORT ON A SERIES OF 484 CASES OF PLAGUE TREATED WITH LUSTIG'S ANTI-PLAGUE SERUM.

By W. M. HAFFKINE, C.I.E.,
Director-in-Chief, Plague Research Laboratory, Bombay.

THE patients were those received into the Bombay Municipal Plague Hospital at Arthur Road, which is under the care of Khan Bahadur N. H. Choksy, M.D. (Hon. causâ, Freiburg), L.M.&S., Special Assistant Health Officer of the Bombay Municipality. The patients were treated by this officer and by Professor Lustig's assistants, who made the serum in Bombay.

Those to whom the serum was administered were selected from the patients proved to be suffering from plague, who were admitted to the Arthur Road Municipal Plague Hospital between the 1st of May 1899 and the 31st of July 1900.

After the diagnosis had been made in the hospital, every second plague patient was at once injected with the serum, while the alternate individuals were kept without this treatment and observed as "controls."

In this way 484 cases diagnosed by competent medical men as plague were treated with this serum, while 484 cases similarly diagnosed and admitted alternately with them were observed for comparison, and not given serum at any time.

All these 968 plague patients were treated in the ordinary symptomatic way, the only difference being the injection of serum in the case of half the number.

The following report is compiled from an examination of the temperature charts kept in the hospital and submitted to me for this purpose by order of Government.

The actual clinical data submitted to analysis are those in which the personality of the observer plays no part, *viz.*, the temperature, the pulse-rate, the number of respirations, the situation of the buboes and the ultimate issue of each case.

The general results may be formulated as follows:—

Among the 484 cases treated with serum there were 55 fewer deaths than among the similar number of control cases.

The first point to ascertain, then, is whether the 484 control patients were from the first, comparable in their main features with the 484 serum cases, and whether the latter would have had more deaths if the serum had been omitted.

There are some indications that this may not have been entirely the case, as the following illustration will show:—

From the first table it appears that the mortality in ordinary plague cases is greatest among those admitted with a high temperature. The higher the

temperature on admission, so much the greater is the mortality. The number of serum treated patients, however, is slightly less in the graver categories, and more in the milder forms; though, indeed, the difference is not great.

From Table II, it is seen that the lowest mortality occurred among patients in whom both pulse and respiration were slow. Of these, the serum cases had 46; the control cases 24. On the other hand, patients in whom the pulse or respiration, or both, were so imperceptible or irregular that they could not be recorded, showed the highest mortality; of these, the control cases had a very considerable preponderance.

Plague cases without buboes, *i.e.*, septicæmic and pneumonic cases, are practically all fatal. From Table III it will be seen that the controls had 29 such cases, while the serum treated cases had only 5. It is evident then that among the serum patients there must have existed a group of 24 cases of a type milder than these cases without buboes.

It is found from Table V that the highest mortality occurs in both sexes between the ages of 21 and 40; but it is seen that the control group had 20 more such cases than the serum group; the numbers being 264 and 244, respectively.

From the same table we learn that the lowest mortality was in males below 15 years of age, and of these the treated cases had more than those not treated; the numbers being 63 and 52, respectively.

As the same individuals figure afterwards in other columns and tables where they are considered from other points of view, the effect of the unequal gravity of the cases will be seen in the form of a lower mortality in each of the categories and sub-divisions in which they are grouped.

It is impossible to maintain that this uneven distribution of cases, which in most instances was quite unavoidable, accounts for the preponderance of deaths observed in the control group, for in certain other sub-divisions showing a lessened but still high mortality, there was a considerable though less preponderance of serum cases. But it is impossible also to say with certainty how many of the excess survivals, if any, are due to the serum. In my original plan of investigation into the efficiency of plague anti-toxic sera, I had foreseen difficulties of this kind, and, as a corrective, added the postulate that in every instance in which a choice has to be made between two patients admitted to hospital at the same time, the more severe case be taken for serum treatment and the milder one for the purposes of control observations.*

If the mortality is influenced favourably in these circumstances, a proof is obtained *à fortiori* of the beneficial action of the treatment applied. In the case under consideration this postulate has not been complied with.

* Note.—This method was actually carried out by Mr. Haffkine at Poona in 1897 in some 200 cases, *vide* Indian Plague Commission Report, Vol. I, p. 14, para. 140; also introduction, page 10, *supra*.—(Ed.)

If we admit that the distribution of patients between the control and serum groups was sufficiently uneven to influence, at least partially, the mortality rates, we must be prepared to find that it played also a part in the difference shown by the two groups in regard to the duration of life in the fatal cases (*vide* Table I, columns 7 and 11).

It was expected that the favourable effect of a serum injection would manifest itself in an immediate or early reduction of the fever temperature. In a number of cases this expectation was not fulfilled; in a large number of others the temperature began to go down after admission to hospital without any serum injection; but when we compare the proportions, we find a favourable difference attributable to the serum, but perhaps partially also to the better condition of the serum cases (Table VI).

This initial favourable effect of the serum was unfortunately not maintained, for when we consider the temperature chart throughout the patients' illness we do not find that the fever left the treated cases sooner than the controls (Table VII), or that in the recovery cases the normal temperature was reached sooner by the serum cases than by the controls (Table VIII).

A paradoxical result is observed in many of the facts recorded. Thus, for instance, femoral buboes gave to the controls a mortality of 79·74 per cent.; serum would seem to have "reduced" it to 55·05 per cent. Cervical glands appear somewhat less fatal (75·86 per cent.), still the serum was much less "successful" here, the serum cases having had a mortality of 73·52 per cent. (Table III).

Similarly patients with multiple neighbouring glands seem to die more frequently (mortality of controls 82·44 per cent.) than those with multiple scattered and opposite glands. Still the serum would seem to have "reduced" the mortality in the first and "increased" it in the two other categories (Table III).

Males are shown in the group under study to recover more frequently than females (Table V); but under the serum treatment a higher proportion of the latter than of the former recovered.

Among the male control cases the highest mortality is found among those between the ages of 21 and 40, while those below 15 years of age show the lowest death-rate. The serum would appear to have been very successful with the first, and to have failed entirely with the second.

The temperature of a plague patient has a natural tendency to go down towards the morning and to rise towards the evening; one might therefore expect that if the serum injection had the virtue of bringing down the temperature, this would be more often manifested in the morning temperatures after evening injections than in the evening temperatures after morning injections. Indeed in

the recovery cases this was so; in the fatal cases it would seem, on the contrary, as if the serum had interfered with the natural morning fall of the fever (Table VI). And so on.

The above paradoxical cases seem to suggest that in the facts observed there were, apart from the serum injections, other factors which influenced the course of the disease and the recovery or death of the patients very powerfully.

Were clinical symptoms actually and effectively improved by the serum, and this improvement maintained for the greater part of the illness, this need not necessarily have led to an improved mortality rate. I may illustrate my meaning by the fact that the injection of water in cholera has a most striking effect on the symptoms, probably such as no other operation has in the case of any other disease; the effect on the mortality appears, however, so absolutely negative that the injections have been abandoned in practice.

Similarly, from the analysis of the plague cases treated with Dr. Terni's curative serum in the Modikhana and Maratha Municipal Plague hospitals, it will be seen that the facts recorded present indications of an improvement effected by the serum in the clinical features of the disease. Notwithstanding this, the mortality rate was 90 deaths in 110 serum cases and 89 deaths in 110 controls.

Considering that the cost of the serum is something like Rs. 60 per patient treated (not patient saved), the results obtained so far from the Lustig, Terni and Brazil sera are not favourable to a general adoption of the treatment.

I beg to acknowledge the able assistance given me by Dr. E. S. Winter of this Laboratory in the laborious task of compiling from the hospital documents the figures reproduced in the tables attached.

Analysis of 968 hospital charts referring to 484 patients treated with Professor Lustig's plague curative serum and 484 alternate cases observed as controls, in the Arthur Road Municipal Plague Hospital, Bombay, under Dr. N. H. Choksy, between May 1899 and July 1900.

I.

			Control cases.				Treated cases.			
			Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).
1. State on admission.	Temperature: Patients whose first recorded temperature was—	Below 99° F.	37	24	64·86	4·27	44	11	25·0	1·68
		99°—100·9°	107	71	66·35	3·16	107	63	58·87	7·13
		101°—102·9°	187	157	83·95	2·60	184	138	75·0	3·74
		103° and above	153	133	86·27	2·40	149	118	79·19	3·13
		Total	484	385	79·55	2·76	484	330	68·18	3·89

II.

			Control cases.				Treated cases.			
			Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days.)	Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).
I.—*contd.* State on admission.	Pulse and respiration. Patients who had on admission—	1. Quick pulse (above 100 in a minute) with quick respiration (above 30 in a minute).	226	186	82·34	3·08	283	204	72·08	3·60
		2. Quick pulse with slow respiration (up to 30 in a minute).	72	53	73·61	2·85	81	54	66·66	7·14
		3. Slow pulse (up to 100 in a minute) with quick respiration.	23	14	60·86	7·53	18	7	38·88	7·71
		4. Slow pulse with slow respiration.	24	10	41·66	7·15	46	12	26·08	4·58
		5. Quick pulse with respiration not recorded.	3	2	66·66	0·50	5	5	100·0	0·10
		6. Pulse not recorded with quick respiration.	24	24	100·0	0·70	18	18	100·0	0·33
		7. Pulse not recorded with slow respiration.	3	3	100·0	0·50	3	3	100·0	0·16
		8. Pulse and respiration not recorded.	109	93	85·32	1·54	30	27	90·0	1·79
			484	385	79·54	2·76	484	330	68·18	3·89

III.

			Control cases.				Treated cases.			
			Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).
I—(*contd.*) State on admission.	Buboes:	Present	455	357	78·45	2·77	479	32)	68·05	3·80
	Patients in whom buboes were found on admission or later on to be—	Single	284	230	80·98	2·12	288	186	64·58	3·14
		Maxillary, single	2	1	50·0	1·50	...	...	...	...
		Cervical, single	29	22	75·86	1·68	34	25	73·52	4·30
		Axillary, single	93	81	86·88	1·88	80	58	72·50	1·84
		Iliac, single	1	1	100·0	23·50	7	4	57·12	0·87
		Inguinal, single	69	55	79·71	2·38	69	44	63·76	4·11
		Femoral, single	79	63	79·74	1·74	89	49	55·05	2·75
		Single in other situations.	11	7	63·63	6·0	9	6	66·66	8·50
		Multiple	171	127	74·26	3·96	191	140	73·29	4·69
		Multiple, neighbouring	131	108	82·44	3·90	149	115	77·18	4·67
		Multiple, opposite	20	11	55·0	0·90	19	11	57·89	2·45
		Multiple, scattered	20	8	40·0	8·81	23	14	60·86	4·53
		Absent altogether	29	28	96·55	1·71	5	4	80·0	10·62

IV.

			Control cases.				Treated cases.			
			Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).
I—(*contd.*) State on admission.	Preventive inoculation.	Inoculated	11	5	45·45	2·0	11	4	36·36	1·75
	Patients who had been previously—	Not inoculated	473	380	80·33	2·71	473	326	68·92	3·91

V.

			Control cases.				Treated cases.			
			Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).
I–(*contd.*) State on admission.	Sex, Age, Caste, Nationality.	Males	354	278	78·53	2·71	351	242	68·94	3·88
	Among the patients there were —	Up to 15 years of age.	52	30	57·69	1·41	63	37	58·73	3·41
		16 to 20	64	50	78·12	3·02	60	45	75·0	5·21
		21 to 40	213	178	83·56	2·62	189	130	68·83	3·20
		Above 40	25	20	80·0	4·62	39	30	76·92	5·40
		Females	130	107	82·30	2·62	133	88	66·16	3·88
		Up to 15 years of age.	51	40	78·43	2·67	39	20	51·28	4·80
		16 to 20	19	15	78·94	1·16	21	14	66·66	5·25
		21 to 40	51	45	88·23	3·18	55	39	70·09	3·76
		Above 40	9	7	77·77	1·92	18	15	83·33	1·73
		Hindoos	410	330	80·48	2·46	408	284	69·58	3·51
		Low caste Hindoos	145	111	76·55	1·95	134	85	63·43	3·45
		Other Hindoos	265	219	82·64	2·31	274	199	72·62	4·09
		Mahomedans	27	20	74·07	7·15	21	14	66·66	3·46
		Goanese and Native Christians.	37	27	72·97	1·72	37	20	54·05	4·40
		Parsis	6	5	83·33	6·30	8	6	75·0	2·0
		Europeans and Eurasians.	4	3	75·0	0·66	10	6	60·0	4·50

VI.

II. Condition of patients after first application of treatment and of their controls.	Serum Cases.			
	A. Number of patients with an admission temperature of 100° F. and over, who were treated with serum immediately on admission and recovered.		B. Number of A whose temperature came down after the first injection of serum and did not again reach the level of admission temperature.	C. Percentage of B. to A.
	* Morning admissions	52	18	34·61
	† Evening admissions	41	21	51·21
	TOTAL	93	39	41·93

(*) Morning admissions = those patients whose first temperature was taken in the morning.
(†) Evening admissions = those patients whose first temperature was taken in the evening.

II.—*contd.*

Condition of patients after first application of treatment and of their controls.

Serum Cases—*contd.*.

A. Number of patients with an admission temperature of 100° F. and over, who were treated with serum immediately on admission and lived for more than 24 hours but eventually died.		B. Number of A whose temperature came down after the first injection of serum and did not again reach the level of admission temperature.	C. Percentage of B. to A.
Morning admissions . .	107	24	22·42
Evening admissions . .	54	8	14·81
TOTAL .	161	32	19·87

Control Cases.

A. Number of patients with an admission temperature of 100° F. and over, and who eventually recovered.		B. Number of A whose temperature came down within 24 hours of admission and did not again reach the level of admission temperature.	C. Percentage of B. to A.
Morning admissions . .	44	9	20·45
Evening admissions . .	26	13	50·0
TOTAL .	70	22	31·42

A. Number of patients with an admission temperature of 100° F. and over, who lived for more than 24 hours after admission but eventually died.		B. Number of A whose temperature came down within 24 hours of admission and did not again reach the level of admission temperature.	C. Percentage of B. to A.
Morning admissions . .	107	15	14·01
Evening admissions . .	79	24	30·37
TOTAL .	186	39	20·96

VII.

III. Condition during treatment.

		Control cases. Number of patients.	Control cases. Number of deaths.	Control cases. Mortality percentage.	Control cases. Average stay in hospital before death (in days).	Treated cases. Number of patients.	Treated cases. Number of deaths.	Treated cases. Mortality percentage.	Treated cases. Average stay in hospital before death (in days).
Temperature:	(*a*) Within 24 hours.	339	281	82·92	1·87	334	246	75·93	2·44
Patients admitted with temperature of 99° F. and above, in whom the temperature, after the first application of treatment (or in controls after admission), reached maximum—	(*b*) Later than 24 hours. (1 treated recovery case counted in "within 24 hours," as the record shows doubtful return.)	108	80	74·07	5·48	116	73	62·93	9·05
	Proportion of (*b*) to (*a*).	31·86 p.cent.	...	...	...	35·80 p. cent.	...	...	...

VIII.

Temperature of twenty patients who recovered (treated and controls) who had the highest admission temperature, and average interval between the first application of treatment or admission to hospital and the time when temperature became for the first time permanently normal :—

III.—*contd.* Condition during treatment.

Control cases.			Serum cases.		
Number of patients.	Admission temperature.	Number of days after admission in which normal temperature became permanent.	Number of patients.	Admission temperature.	Number of days after admission in which normal temperature became permanent.
1	105°—105·9°	12	1	105°—105·9°	3
1	„	36	1	„	22
1	104°—104·9°	11	1	„	26
1	„	14	1	„	12
1	„	24	1	104°—104·9°	9
1	„	26	1	„	25
1	„	8	1	„	44
1	„	19	1	„	15
1	„	2	1	„	14
1	„	4	1	„	47
1	103°—103·9°	11	1	„	41
1	„	73	1	„	41
1	„	15	1	103°—103·9°	1
1	„	17	1	„	14
1	„	20	1	„	1
1	„	11	1	„	35
1	„	12	1	„	2
1	„	17	1	„	16
1	„	34	1	„	33
1	„	33	1	„	29
Average interval		19·95	Average interval		21·05

REPORT ON A SERIES OF 110 CASES OF PLAGUE TREATED WITH TERNI'S ANTI-PLAGUE SERUM.

By W. M. HAFFKINE, C.I.E.,
Director-in-Chief, Plague Research Laboratory,

AND

C. T. COSTELLO, M.B., B.Ch., B.A. (Dublin),
Attached to the Laboratory.

THE patients treated were those admitted to the Modikhana Municipal Plague Hospital, Bombay, between November 1902 and July 1903. This hospital was under the charge of Dr. D. A. Turkhud, M.B., C.M. (Edin.), and the ordinary symptomatic treatment of the cases was carried out by him.

The serum employed was supplied by Professor Terni of Messina and sent for trial through the Secretary of State for India. It was sent out in 10 c.c. bottles, which is presumably the average dose to be given at one time. In reply to an enquiry Professor Terni informed one of us (W. M. Haffkine), that he considered the application of his treatment to some 300 patients would prove its utility, and accordingly sent the requisite amount of serum for this purpose; *viz.*, 1,500 bottles, or an average of 5 bottles, or 50 c.c., for each patient. Four patients received less than this amount (*vide* Table V) because they died before the full quantity could be administered; 42 received 50 c.c. or the prescribed amount; and the rest (65) were given more than this quantity, receiving from 60 to 130 c.c. or above. All were injected hypodermically. The injections were carried out by one of us (C. T. Costello) at the hospital and he also watched the patients and compiled the returns from which the subsequent analysis was made.

The method of selecting the cases was the alternate plan, modified as follows:—

Every alternate patient was treated with Terni's serum unless he—

(*a*) objected to such treatment,
(*b*) was manifestly convalescent,
(*c*) was manifestly moribund, or
(*d*) was proved to be suffering from some disease other than plague.

The number treated with serum was 111, and the number admitted alternately with them was 112. The hundred and twelfth patient (who recovered) not being required, is omitted from the subsequent analysis. Further, the chart of control patient No. 105 having been mislaid in the hospital, it is necessary to omit the corresponding serum-treated case. The number dealt with below is therefore reduced to 110 cases in each category.

When patients coming under the headings (*a*), (*b*), (*c*), (*d*), noted above, were received, they were passed over, and the next admission taken for treatment with or without serum, as the list demanded.

The following is the general result of the analysis of the tables below.

The mortality in the two groups was practically equal, *i.e.*, 89 deaths among 110 cases treated with serum, 90 deaths among 110 not so treated.

The serum-treated cases lived on the average about 8 hours longer than those not treated, *vide* Table I.

The good effects one would expect from an early administration of the remedy are not consistently apparent in Table I.

Similarly inconsistent results are seen in Table II. where patients are grouped according to the apparent severity of the disease. The serum appears to have benefited the severer cases, but not those of a milder type.

Taking the first recorded temperature of the patients as a guide, it is found in the control group that the higher this is, the greater is the death-rate among them. But the serum showed most success in those with a temperature between 101° and 102·9° F., and least in those whose temperature on admission ranged between 99° and 100·9°.

There is no such inconsistency when we consider the patients from the point of view of the pulse and respirations recorded on admission.

The figures referring to the presence or absence of buboes or their position are small, but where they are considerable (single axillary, femoral or inguinal buboes), the result is not consistent. The groups to which the less fatal cases belong do not show improved results under serum treatment.

In the table setting forth the age-distribution, the control cases show the greatest mortality in those above 25 years of age, but it is just in these cases that the serum seems to have had best effect, while in patients below that age where the untreated cases had a lessened mortality, the serum seems to have failed.

From Table III it seems that the first application of serum had some effect in reducing the temperature and pulse-rate within 24 hours after admission;

but unfortunately the mortality appears higher among the treated than among the controls. The injections appear also to have reduced slightly the number of respirations per minute.

Table IV shows that the injections tend to reduce the temperature, pulse and respiration at an earlier date than in the case of the controls, though the mortality is not favourably affected.

Table V shows that the results are not improved by increasing the initial dose, nor by increasing the total amount of serum given.

Those receiving more than 20 c.c. show the highest mortality. There is thus no reason to suppose that better results would be obtained by giving doses larger than those recommended by Professor Terni.

In the year 1904 observations were made on 16 cases of plague admitted to the Maratha Plague Hospital of the Bombay Municipal Corporation.

These were treated hypodermically with Terni's serum in large doses, several hundred c.c. being given in some cases. A similar number of plague cases admitted alternately with them were observed as controls.

The results are shown below:—

	Number.	Deaths.	Mortality per cent.
Serum-treated cases	16	12	75·0
Control cases	16	11	68·75

Analysis of 220 clinical charts referring to 110 plague patients treated with Professors Terni and Bandi's curative serum, and 110 alternate cases observed as controls, in the Modikhana Municipal Plague Hospital, Bombay, under Dr. Turkhud, between November 1902 and July 1903.

I.

		Control cases.				Treated cases.			
		Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).
I. *Previous History.* — Patients who stated they had been ill before admission for—	One day	10	8	80	2·25	8	5	62·50	1·20
	Two days	31	26	83·87	2·51	34	30	88·23	3·70
	Three days	28	23	82·14	2·76	18	11	61·11	3·54
	More than three days	34	26	76·47	4·05	43	36	83·72	3·25
	An unknown time	7	7	100	1·50	7	7	100	2·64
	Total of patients admitted.	110	90	81·81	2·93	110	89	80·90	3·27

II.

		Control cases.				Treated cases.			
		Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).
II. *State on admission.* — General condition of patients,	Drowsy, Comatose or unconscious.	19	19	100·0	1·34	24	21	87·50	1·76
	Not in above condition.	91	71	78·02	3·36	86	68	79·06	3·74
Temperature. Patients who had on admission a temperature of—	Below 99°F.	6	6	100	3·33	11	8	72·72	4·18
	99°—100·9°	20	15	75·0	3·10	22	19	86·36	2·63
	101°—102·9°	52	41	78·84	3·30	44	33	75·0	3·66
	103°—104·9°	31	27	87·09	2·29	29	25	86·20	3·02
	Above 105°	1	1	100	0·50	4	4	100	2·62
	Total	110	90	81·81	2·93	110	89	80·90	3·27
Pulse-rate. Patients whose pulse on admission was, per minute—	90 and below	2	2	100	5·75	2	1	50·0	0·50
	91—120	64	50	78·12	3·30	53	41	77·35	4·86
	121—150	41	35	85·36	2·25	51	43	84·31	1·82
	Above 151	3	3	100	3·0	4	4	100	3·25
	Total	110	90	81·81	2·93	110	89	80·90	3·27
Respiration. Patients whose respiration on admission was, per minute—	35 and less	70	57	81·42	3·07	77	60	77·92	3·59
	36—50	36	30	83·33	2·80	33	29	87·87	1·87
	Above 51	4	3	75·0	1·66	...	...	...	...
	Total	110	90	81·81	2·93	110	89	80·90	3·27

II—*contd.*

		Control cases.				Treated cases.			
		Number of patients.	Number of deaths.	Mortality percentage	Average stay in hospital before death (in days).	Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).
II—*contd.*	Present . .	97	81	83·50	2·95	102	82	80·39	3·24
State on Admission —contd.	Single . .	82	66	80·48	2·40	76	59	77·63	2·65
	Maxillary, single	2	2	100	2·75	...	...	...	...
	Cervical, „	7	7	100	3·50	5	5	100	6·30
	Parotid „	1	1	100	1·50	1	0	0	...
	Axillary „	21	18	85·71	2·05	26	19	73·07	1·89
	Inguina „	18	11	61·11	2·40	12	11	91·66	1·95
Buboes. Patients in whom buboes were found, on admission, or later, to be—	Femoral „	31	26	83·87	2·17	32	24	75·0	2·64
	In other situations single.	2	1	50	0·0	...	...	...	...
	Multiple . .	15	15	100	5·33	26	23	88·46	5·19
	„ neighbouring.	9	9	100	3·88	17	16	94·11	3·22
	„ opposite	1	1	100	1·0	2	2	100·0	1·25
	„ scattered	5	5	100	8·90	7	5	71·42	11·0
	Absent altogether	13	9	69·23	3·61	8	7	87·50	4·35
Sex, age, caste, and nationality. Among the patients there were—	Males . .	90	78	80·11	3·04	102	83	81·37	3·30
	Females . .	20	17	85·0	2·50	8	6	75·0	2·91
	Up to 10 years of age.	8	5	62·50	1·70	5	4	80·0	7·75
	11-25 . .	61	48	78·68	3·34	59	48	81·35	2·96
	26—45 years of age.	38	34	89·47	2·58	39	32	82·05	3·21
	Above 45 .	3	3	100·0	2·50	7	5	71·42	3·0
	Hindus . .	75	61	81·34	2·54	74	65	87·83	3·23
	Mahomedans .	15	12	80·0	4·87	13	9	69·23	1·94
	Goanese and Native Christians.	17	16	94·11	3·15	21	15	71·42	4·23
	Parsis . .	3	1	33·33	0·50	2	...	...	..
	Europeans and Eurasians.	...	...	...	...	...	...	...	...

III.

		Control cases.					Treated cases.				
		Number of patients.	Their proportion to total (per cent.).	Number of deaths.	Mortality percentage.	Average extent of increase or decrease.	Number of patients.	Their proportion to total (per cent.).	Number of deaths.	Mortality percentage.	Average extent of increase or decrease.
III. *Condition of patients after first application of treatment.*											
Duration of Life.											
Died within 24 hours of admission . . .	.....	18	16·36	18	100·0	...	19	17·27	19	100·0	...
Lived for more than 24 hours	.....	92	83·63	72	78·28	...	91	82·72	70	76·92	...
Temperature.											
Total admitted with 100° F. and over, who lived for more than 24 hours .	.....	83	...	64	77·10	...	79	...	63	79·74	...
Patients admitted with temperature above 100° F. in whom the next temperature recorded after treatment (or in controls, after admission), showed—	Increase . .	41	49·40	36	87·80	1·5	32	40·50	28	87·50	1·6
	Decrease . .	38	45·78	26	68·42	1·5	46	58·22	34	73·69	1·9
	Stationary condition . .	4	4·81	2	50·0	...	1	1·26	1	100·0	...
Pulse.											
Total admitted with pulse above 100 a minute, who lived for more than 24 hours	.....	86	...	68	79·06	...	84	...	67	79·76	...
Patients admitted with pulse above 100 a minute, in whom the next number recorded after treatment (or in controls, after admission) showed—	Increase . .	51	59·30	42	82·35	14	36	42·97	32	88·88	15
	Decrease . .	28	32·55	19	67·85	16	39	46·42	28	71·79	12
	Stationary condition . .	7	8·13	7	100·0	...	9	10·71	7	77·77	...

III—*contd.*

		Control cases.					Treated cases.				
		Number of patients.	Their proportion to total (per cent.).	Number of deaths.	Mortality percentage.	Average extent of increase or decrease.	Number of patients.	Their proportion to total (per cent.).	Number of deaths.	Mortality percentage.	Average extent of increase or decrease.
III—*contd.* *Condition of patients after first application of treatment*—contd.											
Respiration.											
Total admitted with more than 28 a minute who lived for more than 24 hours		86	...	68	79·06	...	85	...	68	80·0	...
Patients admitted with more than 28 in a minute in whom the next number recorded after treatment (or in controls, after admission) showed—	Increase . .	49	56·97	42	85·71	6	47	55·29	41	87·23	5
	Decrease . .	30	34·88	21	70·0	5	31	36·47	23	74·19	4
	Stationary condition . .	7	8·13	5	71·42	...	7	8·23	4	57·14	...

IV.

		Control cases.				Treated cases.			
		Number of patients.	Their proportion to total (per cent.).	Number of deaths.	Mortality percentage	Number of patients.	Their proportion to total (per cent.).	Number of deaths.	Mortality percentage.
IV. *Condition of patients throughout the treatment.*									
Temperature.									
	Total .	57	...	38	...	63	...	44	...
Patients admitted with temperature above 100° F., who lived for more than 48 hours, and in whom the temperature after the first application of treatment (or, in controls, after admission), reached maximum.	Within 24 hours	15	26·31	9	60·0	24	38·09	15	62·50
	Later than 24 hours . .	42	73·68	29	69·04	39	61·90	29	74·35

IV—*contd.*

		Control cases.				Treated cases.			
		Number of patients.	Their proportion to total (per cent.).	Number of deaths.	Mortality percentage.	Number of patients.	Their proportion to total (per cent.).	Number of deaths.	Mortality percentage.
IV—*contd.*									
Condition of patients throughout the treatment—contd.	TOTAL .	59	...	41	...	64	...	46	...
Pulse.									
Patients admitted with pulse above 100 in a minute, who lived for more than 48 hours, and in whom the number after first application of treatment reached maximum.	Within 24 hours	8	13·55	3	37·50	13	20·31	6	46·15
	Later than 24 hours . .	51	86·44	38	74·50	51	79·68	40	78·43
	TOTAL .	60	...	42	...	63	...	45	...
Respiration.									
Patients admitted with more than 28 per minute, who lived for more than 48 hours, and in whom the number recorded after first application of treatment reached maximum.	Within 24 hours	6	10·0	2	33·33	11	17·46	6	54·54
	Later than 24 hours.	54	90·0	40	74·07	52	82·53	39	75·0
Temperature.									
Patients who ultimately recovered, and who after their temperature had reached normal, had a secondary rise to above 99°F. within a fortnight of their admission.	.....	9	45·0	...	...	6	28·57	...	...

IV—*concld.*

Highest temperature, pulse, and respiration of all recovery cases (Treated and Controls).

	Control cases.			Treated cases.		
	Highest temperature.	Highest pulse.	Highest respiration.	Highest temperature.	Highest pulse.	Highest respiration.
IV—*concld.*	105·0	154	52	103·0	148	52
Condition of patients throughout the treatment—concld.	101·6	158	40	99·0	134	40
	103·6	180	60	98·8	104	28
	101·5	160	44	103·4	104	33
	99·8	104	45	103·5	140	48
	103·6	126	42	103·8	126	30
	103·8	146	40	104·6	128	36
	102·6	118	30	104·0	140	48
Temperature—*concld.*	104·0	164	40	101·6	126	40
	101·8	128	40	103·2	120	40
The highest temperature, pulse and respiration recorded in discharged patients.	102·0	128	34	103·6	134	46
	102·6	124	40	102·6	120	40
	104·6	150	45	103 0	112	36
	104·4	158	44	103·6	140	36
	103·0	128	34	100·4	116	28
	103·6	140	48	100·6	108	30
	101·8	120	32	102·0	120	37
	104·4	134	40	104·4	140	41
	102·0	108	28	103·6	124	34
	102·2	120	52	104·0	148	40
	...	...	...	102·4	116	28
Average .	102·8	138	41	102·6	127	37

V.

Doses of serum injected.

Initial dose given.	Total number of patients.	Deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Recoveries.	Average stay in hospital before discharge (in days).
10 c.c. . . .	4	3	75·0	4·16	1	28
20 „ . . .	19	14	73·68	5·03	5	40

V.

Doses of serum injected—contd.

Initial dose given.	Total number of patients.	Deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Recoveries.	Average stay in hospital before discharge (in days).
25 c.c.	1	...	...	...	1	66
30 „	56	45	80·35	2·96	11	41·54
40 „	20	17	85·0	4·29	3	60·0
50 „	3	3	100·0	0·33	...	...
60 „	6	6	100·0	0·41	...	...
100 „	1	1	100·0	0·16	...	...

Amount of serum injected.

Amount of serum given.	Total number of patients.	Deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Recoveries.	Average stay in hospital before discharge (in days).
20 c.c.	3	3	100·0	0·50	...	...
30 „	1	1	100·0	0·50	...	...
50 „	42	33	78·57	4·09	9	50·64
60 „	6	6	100·0	0·41	...	...
70 „	32	26	81·25	2·61	6	39·0
80 „	5	2	40·0	1·25	3	61·0
100 „	6	5	83·33	1·90	1	43·0
110 „	1	1	100·0	0·50	...	...
120 „	9	9	100·0	4·11	...	...
Over 130 c.c.	5	3	60·0	12·0	2	28·50

REPORT ON A SERIES OF 70 CASES OF PLAGUE TREATED WITH BRAZIL'S ANTI-PLAGUE SERUM.

By W. M. HAFFKINE, C.I.E.,
Director-in-Chief, Plague Research Laboratory,

AND

W. G. WEST, M.R.C.S. (Eng.), L.R.C.P. (Lond.), M.D. (Geneva),
Attached to the Laboratory.

THE serum used in this series of cases was prepared by Dr. Vital Brazil, Director of the State Sero-therapeutic Institute of San Paulo, Brazil, and sent out for trial by the Secretary of State in August 1903.

The serum was supplied in sealed test-tubes each containing about 20 c.c. Of these, 600 were received and stored in an ice-box till February, when a sufficient number of patients began to come to the hospitals. The patients treated were those admitted to hospital between the 10th of February and the end of March 1904. Fifty were treated in the Maratha Municipal Plague Hospital (in charge of Dr. N. H. Choksy) and 20 in the Modikhana Municipal Plague Hospital (in charge of Dr. D. A. Turkhud). These medical men were responsible for the ordinary symptomatic treatment, which was used for all cases whether or not they also received the serum treatment.

Every alternate patient received serum treatment, the others being kept to serve as controls. In the Modikhana hospital, which received a somewhat different class of patients, several (79, with a subsequent mortality of 67·1 per cent.) refused to undergo the serum treatment. In such circumstances the serum was offered to the next patient admitted until one was found willing to undergo the treatment, when the next case was taken as a control case. This did not disturb the experiment to any extent; but more difficulty was found with patients admitted with no definite symptoms of plague. These had to be kept separate till a definite diagnosis was arrived at. The procedure was thus the same as in the trial of Terni's serum (*vide* p. 37).

The serum injections, which in all cases were hypodermic, were given by one of us (W. G. West), who was likewise responsible for the correctness of the history of each patient, as observed by him at the hospitals.

The initial dose injected was 40 c.c. in all the cases (20 in number) treated in the Modikhana Hospital, while in the Maratha Hospital two cases received 20 c.c., six received 40 c.c., while the remainder (42) got 60 c.c. The doses were repeated once in 24 hours, so that those who lived for some time, or recovered, received as much as 340 to 360 c.c. in some cases. This method

of administration was generally in accordance with the instructions sent by Dr. Brazil.

The tables below show the results obtained in the two hospitals :—

MODIKHANA HOSPITAL.

	No. of patients.	Deaths.	Percentage of mortality.
Serum-treated	20	17	85
Control cases	20	15	75

MARATHA HOSPITAL

	No. of patients.	Deaths.	Percentage of mortality.
Serum-treated	50	41	82
Control cases	50	45	90

The small difference in these results, in one case in favour of the controls, and in the other in favour of those treated with serum, would appear to be accounted for by the chance inclusion (Table II) of a few more serious cases on the one side than on the other.

In both hospitals the serum appears in several cases to have acted by reducing the temperature and pulse-rate within the first few hours after admission. In the Maratha Hospital the rate of breathing was reduced also in some cases. In the Modikhana Hospital these cases showed a greater mortality than the control cases, while in the Maratha Hospital the contrary was the case.

In both hospitals the fatal serum cases lived longer than the fatal control cases. In the Modikhana Hospital, where the serum-treated cases showed a higher mortality than the controls, they lived on the average 2·55 days longer. In the Maratha Hospital, where the serum-treated cases showed a lower mortality than the controls, they lived on the average only $7\frac{1}{2}$ hours longer.

As regards the few recovery cases, the normal state as regards temperature, pulse and respiration was sooner attained in the case of the serum-treated cases than in the controls in the Modikhana Hospital, while in Maratha Hospital the reverse was the case.

The type of case admitted to hospital during the time of trial of the serum was severe, but the above does not warrant us in ascribing to the treatment any measure of influence on the course of the disease.

Analysis of one hundred hospital charts referring to 50 patients treated with Dr. Brazil's plague curative serum and 50 alternate cases observed as controls in the Maratha Municipal Plague Hospital, Bombay, under Dr. N. H. Choksy, in 1904—

I.

		Control cases.				Treated cases.			
		Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).
I. *Previous History.* Patients who stated they had been ill before admission for—	1 day . .	1	0	...	...	1	1	100	2·00
	2 days . .	10	9	90	2·63	12	10	83·33	2·80
	3 days . .	13	13	100	2·66	17	15	88·23	2·43
	More than 3 days.	19	16	84·21	2·13	16	12	80	3·09
	An unknown time.	7	7	100	1·21	4	3	75	1·26
	Total of patients admitted.	50	45	90	2·25	50	41	82	2·56

II.

		Control cases.				Treated casse.			
		Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).
II. *State on admission.* General condition of patients—	Moribund .	10	10	100	·55	10	10	100	·50
	Neither moribund nor convalescent	40	35	87·50	2·8	40	31	77·50	2·46
	Drowsy, comatose or unconscious.	21	21	100	2·47	22	19	86·36	3·15
	Not in above condition.	19 ...	14	73·68	3·42	18	12	66·66	3·36

		Control cases.				Treated cases.			
		Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).
II—*contd.*									
***State on admission*—contd.**	Below 99° F.	...	...	...	...	4	2	50	0·2
	99—100·9°	7	6	85·71	2·33	7	7	100	2·21
Temperature.	101—102·9°	19	16	84·21	2·75	19	16	84·21	2·40
Patients who had, on admission, a temperature of—	103—104·9°	22	21	95·45	2·16	20	16	80	2·93
	Above 105°	2	2	100	...	...	...	...	...
	TOTAL	...	...	...	...	...	...	...	...
Pulse-rate.	90 and below	...	...	...	...	2	1	50	...
Patients whose pulse, on admission, was, per minute,—	91—120	25	21	84	2·21	20	16	80	4·25
	121—150	23	22	95·65	2·36	22	18	81·81	1·97
	Above 151	2	2	100	·50	6	6	100	·66
	TOTAL	...	...	...	...	...	...	...	...
Respiration.									
Patients whose respiration, on admission, was, per minute,—	35 and less	24	19	79·16	2·44	30	22	73·33	3·11
	36—50	26	26	100	2·19	20	19	95	2·05
	Above 51	...	...	...	...	...	...	...	...
	TOTAL	...	...	...	...	...	...	...	...
Buboes.									
Patients in whom buboes were found, on admission, or later, to be—	Present	50	45	90	2·25	50	41	82	2·56
	Single	12	10	83·33	2·20	8	6	75	2·33
	Maxillary, single	...	...	...	...	...	...	...	...
	Parotid „	...	...	...	...	...	...	...	...
	Cervical „	...	...	...	...	2	2	100	4
	Axillary „	9	8	88·88	2·25	5	3	60	2
	Iliac „	...	...	...	...	1	1	100	...
	Inguinal „	...	...	...	...	...	...	...	...

		Control cases.				Treated cases.			
		Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).
II—*concld.*	Femoral, single .	3	2	66·66	2	...	...	...	...
State on admission—concld.	In other situations, single.	...	...	...	...	...	...	...	...
Buboes.	Multiple . .	38	35	92·10	2·20	42	35	83·33	2·67
Patients in whom buboes were found, on admission, or, later, to be—	Multiple, neighbouring.	27	25	92·55	2·26	34	29	85·26	2·67
	Multiple, opposite.	2	2	100	2·	4	4	100	1·88
	Multiple, scattered.	9	8	88·88	3	4	2	50	4·25
	Absent altogether.	...	...	...	...	...	...	...	...
Microbes in blood.	0 days after .	1	1	100	...	...	...	...	...
Patients examined in whom microbes were found, on admission to hospital, to be present and who lived for—	1 day „ .	6	6	100	1·25	4	4	100	1·38
	2 days „ .	2	2	100	2	4	4	100	2·0
	3 and more after	6	6	100	3·75	5	5	100	4·10
	Recovered .	...	...	...	...	...	...	...	...
	Microbes not found in.	27	22	81·48	2·50	24	15	62·15	2·13
	Not examined .	8	8	100	1·82	13	13	100	3·19
Sex, age, caste and nationality.	Males . .	44	39	88·63	2·35	40	31	77·50	2·37
Among the patients there were—	Females . .	6	6	100	1·83	10	10	100	3·4
	Up to 10 years of age.	3	2	66·66	1·25	2	1	50	1·5
	11—25 . .	30	27	90	2·70	29	22	81·48	2·61
	26—45 . .	15	14	93·33	1·82	15	14	93·33	2·32
	Above 45 .	2	2	100	1·5	4	4	100	3·63
	Hindoos . .	41	37	90·24	2·31	38	34	89·47	2·83
	Mahomedans .	5	5	100	2·90	10	6	60	1·33
	Goanese and Native Christians.	4	3	75	1·16	2	1	50	1·50
	Parsis . .	...	...	...	...	...	...	...	...
	Europeans and Eurasians.	...	...	...	...	...	...	...	...

III.

		Control cases.					Treated cases.				
		Number of patients.	Their proportion to total (percentage).	Number of deaths.	Mortality percentage.	Average extent of increase or decrease.	Number of patients.	Their proportion to total (percentage).	Number of deaths.	Mortality percentage.	Average extent of increase or decrease.
...											
... III.											
Condition of patients after first application of treatment.											
Lived for more than 24 hours . . .	...	45	90	40	88·88	...	45	90	36	80	...
Temperature.											
Total admitted with 100° F. and over, who lived for more than 24 hours .	...	37	...	32	86·49	...	34	...	27	79·41	...
Patients admitted with temperature above 100° F., in whom the next temperature, recorded after treatment (or, in controls, after admission), showed—	Increase . .	19	51·35	16	84·21	1·41	10	29·41	9	90	1·42
	Decrease . .	18	48·65	16	88·88	2·41	20	58·82	15	75	2·62
	Stationary condition .	...	...	...	...	...	4	11·76	3	75	...
			...								
Pulse.											
Total admitted with pulse above 100 a minute, who lived for more than 24 hours	...	36	...	32	88·89	...	33	...	26	78·78	...
Patients admitted with pulse above 100 a minute, in whom the next number, recorded after treatment (or, in controls, after admission), showed—	Increase . .	18	50	6	88·88	8·66	9	27·27	8	88·88	9·90
	Decrease . .	15	41·67	14	93·33	5·60	19	57·58	14	73·68	9·60
	Stationary condition .	3	8·33	2	66·66	...	5	15·15	4	80	...
Respiration.											
Total admitted with more than 28 a minute who lived for more than 24 hours	...	37	...	32	86·49	...	33	...	26	78·79	...
Patients admitted with more than 28 in a minute, in, whom the next number, recorded after treatment (or, in controls, after admission), showed an—	Increase . .	15	40·54	13	86·66	2·40	15	45·45	12	80	3·31
	Decrease . .	12	32·43	12	100	4·40	13	39·39	9	69·23	5·39
	Stationary condition .	10	27·03	7	70	....	5	15·15	5	100	...

IV.

		Control cases.				Treated cases.			
		Number of patients.	Their proportion to total (percentage).	Number of deaths.	Mortality percentage.	Number of patients.	Their proportion to total (percentage).	Number of deaths.	Mortality percentage.
IV. *Condition of patients throughout the treatment.*									
Temperature. Patients admitted with temperature above 100°F., who lived for more than 48 hours, and in whom the temperature, after the first application of treatment (or, in controls, after admission), reached maximum—	Total .	25	...	20	80·0	23	...	16	69·56
	Within 24 hours	16	64	12	75	14	60·87	9	64·28
	Later than 24 hours.	9	36	8	88·88	9	39·13	7	77·77
	Total .	25	...	20	80	23	...	16	69·56
Pulse. Patients admitted with pulse above 100 in a minute, who lived for more than 48 hours, and in whom the number, after first application of treatment (or, in controls, after admission), reached maximum.	Within 24 hours	15	60	10	66·66	16	69·57	13	81·25
	Later than 24 hours.	10	40	10	100	7	30·43	3	42·85
	Total .	24	...	19	79·17	23	...	16	69·56
Respirations. Patients admitted with more than 28 per minute, who lived for more than 48 hours, and in whom the number recorded, after first application of treatment (or, in controls, after admission), reached maximum—	...								
	Within 24 hours	10	41·67	6	60	8	34·78	6	75
	Later than 24 hours.	14	58·33	13	92·85	15	65·22	10	66·66
Temperature. Patients who ultimately recovered and who, after their temperature had reached normal, had a secondary rise above 99° F. within a fortnight of their admission .	...	...	...	...	...	4	9·76	...	...
Pulse. Patients who ultimately recovered and who, after their pulse-rate became normal, had a relapse to above 90 in a minute .	...	...	...	...	...	4	9·76	...	..
Respiration. Patients who ultimately recovered and who, after their respiration became normal, had a relapse to above 35 in a minute .	...	...	...	...	...	2	4·88	...	...

V.

Recovery cases: Interval between admission to hospital and the time when the temperature, pulse, and respiration become normal.

	Control cases.	Treated cases.
Temperature	5·90 days	9·64 days.
Pulse-rate	5·55 „	8·42 „
Respiration	6·66 „	9·42 „

VI.

Average stay in hospital of fatal cases.

Control cases.	Treated cases.
2·25 days.	2·56 days.

VII.

Doses of serum injected (subcutaneously) into the 50 patients treated.

Initial dose injected (in c.c.).	Total quantity injected (in c.c.).	Number of patients so injected.	Number of recoveries among them.	Number of deaths among them.
20	20	1	...	1
20	40	1	...	1
40	40	1	...	1
60	60	15	...	15
20	80	1	1	...
40	100	1	...	1
40	120	1	...	1
60	120	8	...	8
20	140	1	1	...
60	180	5	...	5
60	200	1	...	1
60	240	4	...	4
40	260	1	1	...
60	260	1	1	...
60	280	3	2	1
60	340	2	2	...
60	350	1	...	1
60	360	2	1	1

Analysis of Forty clinical charts referring to 20 patients treated with Dr. Brazil's plague curative serum and 20 alternate cases observed as controls, in the Modikhana Municipal Plague Hospital in Bombay, under Dr. Turkhud, in 1904.

I.

		Control cases.				Treated cases.			
		Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).
I. *Previous history.* Patients who stated they had been ill before admission for—	1 day . .	3	2	66·66	·66	...	...	...	...
	2 days . .	5	1	20	3·50	4	4	100	7·25
	3 days . .	4	4	100	2·87	8	6	75	3·58
	More than 3 days	8	8	100	1·75	7	6	85·71	4·25
	An unknown time . .	...	...	...	....	1	1	100	2·5
	Total of patients admitted .	20	15	75	2·06	20	17	85	4·61

II.

II. *State on admission.* General condition of patients.	Moribund .	3	3	100	·66	3	3	100	·66
	Convalescent .	...	...	...	...	...	...	...	...
	Drowsy . .	7	5	71·42	2·10	8	8	100	3·67
	Comatose .	...	...	...	...	1	1	100	1
	Unconscious .	2	2	100	2·25	1	1	100	3·5
	Not in above condition .	8	5	62·50	2·80	7	4	57·14	6·12
Temperature. Patients who had, on admission, a temperature of—	Below 99° F. .	1	1	100	3·50	1	1	100	3·50
	99—100·9° F. .	2	2	100	2·25	...	...	...	...
	101—102·9° F. .	10	7	70	2·57	10	9	90	4·11
	103° and above .	7	5	71·45	1·60	9	7	77·77	5·42
Pulse-rate. Patients whose pulse, on admission, was, per minute,—	90 and below .	...	...	...	...	1	1	100	2·5
	91—120 . .	13	10	76·92	1·95	4	2	50	1·50
	121—150 . .	7	5	71·42	2·3	15	14	93·33	5·17
	Above 151 .	...	...	...	...	...	...	...	...
Respirations. Patients whose respiration, on admission, was per minute,—	35 and less .	17	13	76·47	2·15	16	13	81·25	5·34
	36—50 . . .	3	2	66·66	1·50	4	4	100	2·35
	Above 51 .	...	...	...	...	...	...	...	...

		Control cases.				Treated cases.			
		Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).
II—*contd.*	Present . .	18	14	77·77	2·07	20	17	85	4·61
	Single . .	12	9	75	2·05	10	8	80	6·62
	Maxillary, single	...	...	...	...	...	...	...	...
	Cervical „ .	...	...	...	...	...	...	...	...
State on admission.	Axillary „ .	4	4	100	2·50	5	3	60	1·83
Buboes,	Iliac „ .	1	1	100	2·50	1	1	100	20
Patients in whom buboes were found, on admission or later on, to be—	Inguinal „ .	2	1	50	1·5	...	...	...	...
	Femoral „ .	4	3	75	1·50	2	2	100	3·25
	Parotid „ .	1	...	...	...	2	2	100	10·5
	Multiple „ .	6	5	83·33	2·10	10	9	90	2·83
	Multiple, neighbouring .	3	2	66·66	2·75	8	8	100	2·74
	Multiple, opposite	...	...	...	...	...	...	...	...
	Multiple, scattered . .	3	3	100	2	2	1	50	3·50
	Absent altogether . .	2	1	50	1	...	...	...	...
Microbes in blood.									
Patients examined in whom microbes were found, on admission to hospital, to be—	Present . .	5	5	100	2·20	4	4	100	2·35
	Absent . .	5	2	40	2·50	4	3	75	3·62
Sex, age, caste, nationality.									
Among the patients there were—	Males up to— 15 years of age	5	4	80	2·87	1	1	100	7
	16—20 .	6	3	50	2·16	6	6	100	7·41
	21—40 .	7	6	85·71	1·70	8	6	75	2·66
	Above 41 .	1	1	100	1·50	2	2	100	4·50
	Females up to— 15 years of age	...	...	...	...	1	...	...	...
	16—20 .	1	1	100	3	...	...	...	...
	21—40 .	...	...	...	...	1	1	100	1
	Above 41 .	...	...	...	...	1	1	100	1
	Hindoos . .	11	7	63·63	1·92	11	10	90·90	4·65
	Mahomedans .	3	3	100	1·66	2	1	50	...
	Goanese and Native Christians . .	6	5	83·33	2·50	7	6	85·71	5·33

III.

		Control cases.				Treated cases.			
		Number of patients.	Number of deaths.	Mortality percentage.	Average extent of increase or decrease.	Number of patients.	Number of deaths.	Mortality percentage.	Average extent of increase or decrease.
III. *Condition of patients after first application of treatment.*									
Temperature.									
Patients admitted with temperature above 99° F., in whom the next temperature, recorded after treatment (or, in controls, after admission), showed an—	Increase . .	12	10	83·3	1·4	10	8	80	1·1
	Decrease . .	3	1	33·3	1·4	8	7	87·50	2·05
	Stationary condition . .	3	2	66·6	...	...	...	...	...
Pulse.									
Patients admitted with pulse above 100 a minute, in whom the next number recorded after treatment (or in controls, after admission), showed—	Increase . .	13	9	69·1	11·3	8	8	100	10·7
	Decrease . .	3	2	66·66	12·6	5	5	100	10·6
	Stationary condition . .	1	1	100	...	2	1	50·0	...
Respiration.									
Patients admitted with more than 28 a minute, in whom the next number recorded after treatment (or, in controls, after admission), showed an—	Increase . .	2	2	100	6	1	1	100	12
	Decrease . .	3	2	66·6	8·3	2	2	100	6
	Stationary condition . .	1	1	100	...	...	...	...	...

IV.

		Control cases.			Treated cases.		
		Number of patients.	Number of deaths.	Mortality percentage.	Number of patients.	Number of deaths.	Mortality percentage.
IV.							
Condition of patients throughout the treatment.							
Temperature.							
Patients admitted with temperature above 99°F., who lived for more than 48 hours, and in whom the temperature, after the first application of treatment (or, in controls, after admission), reached maximum—	Within 24 hours	8	5	62·5	6	5	83·33
	Later than 24 hours.	5	3	60·0	7	5	71·42
Pulse.							
Patients admitted with pulse above 100 in a minute who lived for more than 48 hours, and in whom the number, after first application of treatment (or, in controls, after admission), reached maximum—	Within 24 hours	4	2	50·0	1	1	100
	Later than 24 hours.	10	7	70·0	11	10	90·90
Respiration.							
Patients admitted with more than 28 per minute, who lived for more than 48 hours, and in whom the number recorded, after first application of treatment (or, in control, after admission), reached maximum.	Within 24 hours	1	1	100·0	...	...	...
	Later than 24 hours.	2	1	50·0	2	2	100·0

V.

Recovery cases (treated and controls): average interval between application of treatment or admission to hospital, and the time when (1) temperature, (2) pulse, and (3) respirations became for the first time normal.

	Control cases.	Treated cases.
Temperature	7·20 days	7 days
Pulse	9·32 „	6·33 „
Respirations	6·66 „	6·33 „

VI.

Amount of serum injected (subcutaneously) into the 20 patients.

	Total of serum injected.	Initial dose injected on admission.
Patient 1,	80 c.c. injected in the vicinity of bubo—died . .	40 c.c.
„ 2,	40 c.c. injected in the vicinity of bubo—died . .	40 c.c.
„ 3,	240 c.c. injected in the vicinity of bubo—died . .	40 c.c.
„ 4,	200 c.c. injected in the vicinity of bubo—died . .	40 c.c.
„ 5,	40 c.c. injected in the vicinity of bubo—died . .	40 c.c.
„ 6,	120 c.c. injected in the vicinity of bubo—cured . .	40 c.c.
„ 7,	160 c.c. injected in the vicinity of bubo—died . .	40 c.c.
„ 8,	60 c.c. injected in the vicinity of bubo—died . .	40 c.c.
„ 9,	80 c.c. injected in the vicinity of bubo—died . .	40 c.c.
„ 10,	200 c.c. injected in the vicinity of bubo—died . .	40 c.c.
„ 11,	600 c.c. injected in the vicinity of bubo—died from peritonitis due to iliac bubo . .	40 c.c.
„ 12,	340 c.c. injected in the vicinity of bubo—died . .	
„ 13,	140 c.c. injected in the vicinity of bubo—died . .	40 c.c.
„ 14,	340 c.c. injected in the vicinity of bubo—cured . .	40 c.c.
„ 15,	40 c.c. injected in the vicinity of bubo—died . .	40 c.c.
„ 16,	140 c.c. injected in the vicinity of bubo—died . .	40 c.c.
„ 17,	340 c.c. injected in the vicinity of bubo—cured . .	40 c.c.
„ 18,	260 c.c. injected in the vicinity of bubo—died . .	40 c.c.
„ 19,	280 c.c. injected in the vicinity of bubo—died . .	40 c.c.
„ 20,	80 c.c. injected in the vicinity of bubo—died . .	40 c.c.

REPORT ON A SERIES OF 68 CASES OF PLAGUE TREATED WITH ROUX' ANTI-PLAGUE SERUM.

By W. G. WEST, M.R.C.S. (Eng.), L.R.C.P. (Lond.), M.D. (Geneva),
Attached to the Plague Research Laboratory, Bombay.

THE serum was sent from the Pasteur Institute, Paris, in the middle of March 1904, by Dr. Roux, in response to a telegram from Mr. Haffkine, and was received here in the beginning of the following month. Twenty litres of serum were sent out in bottles containing 100 c.c. each, secured by India-rubber caps and stoppers.

The experiment was in all its details planned by Mr. Haffkine, before his departure from India, but the watching of the patients and administration of the serum was carried out in hospital by the present writer.

The patients treated were those admitted to the Maratha Municipal Plague hospital (under the care of Dr. N. H. Choksy) between the 8th of April and the 5th of May 1904. Between these dates 160 cases were admitted, 80 were placed in the serum group and 80 alternate cases in the control group. Twelve patients of the serum group were either moribund or convalescent on admission and were therefore not injected. These 12 cases, as well as the 12 corresponding control cases, have therefore been excluded from the 160 cases, thus leaving a total of 68 cases on each side.

As regards the doses given, Professor Roux' recent recommendations (*vide* page 63, Roux' letter) were as far as possible carried out, *viz.*:—

(i) Subcutaneously, large doses were injected, the initial dose for an adult being in the large majority of cases 100 c.c. followed in 12 hours by a similar quantity. The total quantity of serum injected generally amounted to 300 c.c. and more.

(ii) Intravenously, the initial dose was in the greater number of cases 40 c.c., followed by another injection of the same quantity 12 hours later, the total quantity of serum injected intravenously amounting generally to about 120 c.c.

Of the 68 serum-injected patients—

(*a*) 43 were injected only subcutaneously, the initial dose being (as before mentioned) mostly 100 c.c. and the total up to 300 or more, and in one case 700 c.c. Of these, 29 died, giving a mortality of 67·44 per cent. ;

(*b*) 12 patients were injected both subcutaneously and intravenously, the initial injection in these patients being done subcutaneously. Of these, 8 died, giving a mortality percentage of 66·66 per cent. and, lastly,—

(*c*) 13 patients had initial injections into the veins of 40 c.c. followed in 12 hours by another injection of the same quantity; some few of these cases were also injected subcutaneously, the total quantity of serum injected amounting in some cases to 400 and 500 c.c. Of this group, 8 died, giving a mortality of 61·53 per cent.

Among the 68 cases treated by the serum, there were 45 deaths, whereas, among the 68 cases not so treated (control cases), there were 41 deaths.

The serum cases thus show a death-rate of 66·17 per cent., whereas the control cases have a death-rate of 60·29 per cent., a difference in favour of the control cases of 5·86 per cent.

In studying the attached tables, the chief point appears to be—Were the larger number of the more serious cases in the group of the serum-treated patients or not?

With regard to the general condition of the patient on admission (*vide* Table II), it will be noticed that there were ten patients in such a feeble condition that these were classed among the moribund in the serum group, whereas there were only four such cases among the control group. But, on the other hand, there were 16 cases in the control group admitted in a comatose condition, all of whom died, whereas there were only six such among the serum cases. The distinction between "comatose" and "moribund" patients, however, was one difficult to settle in the hospital, and it seems better to amalgamate these two headings. If this be done, we find 20 patients comatose and moribund on the control side, and 16 similarly conditioned on the treated side.

Taken as a whole, then, the conditions were slightly against the non-treated cases under this head.

With regard to the sex of the patient, it will be noted that the highest mortality occurred on the side of the males; of these, the serum cases had a preponderance, the figures being 54 and 48, respectively.

Also with reference to the age of the patient, the highest mortality occurred in those patients of 46 years and over. In this group the serum cases had five cases, the control cases one.

Then, again, with regard to the nationality of the patient, the highest mortality occurred among the Goanese and Native Christians; here the serum cases had a preponderance of six cases, the numbers being 4 and 10, respectively.

Similarly with regard to the finding of microbes in the blood on date of admission, the serum group had 19, while the control group had 8 only.

The method adopted for demonstrating microbes in the blood was as follows :

A small capsule of blood was taken from the patient, sealed up and sent to the laboratory.

This blood was then placed in a watch glass, mixed with sterile salt solution and injected subcutaneously into a rat, by one of the laboratory officials.

When the rat died, an examination by spleen smear and culture from the heart blood was made to ascertain the presence or absence of plague germs.

It is unfortunate that owing to pressure of work in the laboratory the examination of the rats dying after injection could not be carried out in a regular manner. Such entries as "rat decomposed" occur frequently in the records, and it is therefore impossible to say that the ratio of 8 to 19 represents the true proportion of septicæmic cases in the two groups.

As the cases were chosen impartially, it seems incredible that such a large proportion of septicæmic cases should have found their way into the serum group. But the fact remains that this is so, and it must be kept in mind in reckoning the results of treatment in this series of cases.

All the tables appear to demonstrate that, although no reduction of the mortality could be attributed to the treatment, yet life was prolonged in many cases.

That the initial effect of the serum had the power of reducing the temperature, pulse and respirations would appear to be probable, *vide* Table III, but this favourable initial effect was not maintained.

Copy of a letter from Professor Roux, Paris, to W. M. Haffkine, Esq., C.I.E., Director-in-Chief, Plague Research Laboratory, Bombay; dated Paris, the 25th March 1904.

" MON CHER DR. HAFFKINE,

" En réponse à votre télégramme je vous ai fait expedier 10 litres de sérum antipesteux en flacons de 100 c.c. Ce sérum a donné d'excellents résultats à Marseille chaque fois que nous l'avons essayé et aussi au Brésil, en République Argentine, et au Mexique. Ce dont il faut être bien convaincu c'est que les grandes doses sont nécessaires. Les médecins veulent toujours employer le sérum antipesteux comme ils employent le sérum anti-diphtérique et ils n'ont que de mauvais effets.

" La peste et la diphtérie ne sont pas des maladies comparables et le sérum antipesteux n'agit pas à la manière du sérum anti-diphtérique. Si vous voulez guérir vos pestifères, injectez 100 c.c. en une seule fois et réitérez l'injection dans les 12 heures. Ne craignez pas d'injecter en tout 300 et plus.

" L'injection intra-veineuse demande moins de sérum et est plus efficace. Une première injection de 40 c.c. suivie d'une seconde de même quantité quelques heures après suffit le plus souvent.

" Mais cette petite opération doit être faite avec soin ; il faut faire tièdir le sérum, s'assurer qu'il n'y a pas trace de dépôt et pousser l'injection très lentement en interrompant à la moindre gêne respiratoire. Les médecins redoutent ces injections intra-veineuses qui ont si bien réussi à Calmette et à Salimbeni lors de l' épidémie de Porto.

" Vous serez bien aimable, mon cher Haffkine, de me dire ce qui arrivera de vos essais de séro-thérapie pesteuse.

" Recevez, je vous prie, l'assurance de mes sentiments les meilleurs et les plus dévoués."

(Sé.) DR. ROUX.

Analysis of Sixty-eight clinical charts of patients under treatment with Roux serum.

I.

		Control cases.				Treated cases.			
		Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).
I. *Previous history.* Patients stated to have been ill before admission for—	1 day	3	...	...	...	3	1	33·33	2
	2 days	14	8	57·14	3·75	24	19	79·16	6·63
	3 days	31	23	74·19	3·13	19	12	63·15	3·33
	More than 3 days.	20	10	50	7	20	13	65	13·30
	Unknown time	...	...	...	...	2	...	...	...
	Total of patients admitted.	68	41	60·29	4·19	68	45	66·17	7·57

II.

II.									
State on admission. General condition of patients included in the trial who, on admission were—	Drowsy	19	12	63·15	4·16	21	14	66·66	9·03
	Comatose or unconscious.	16	16	100	2·15	6	6	100	2·33
	Moribund	4	4	100	50	10	10	100	1·40
	Not in above condition.	29	9	31·03	9·50	31	15	48·38	12·56
Temperature. Patients who had, on admission,—	Below 99° F	4	2	50	8·75	3	1	33·33	1·50
	99°—100·9°	13	7	53·07	1·85	15	10	66·66	6·65
	101°—102·9°	29	21	72·22	3·52	31	20	64·51	8·81
	103°—104·9°	22	11	50	6·13	19	14	73·67	6·85
	105° and above	...	...	...	...	...	...	...	...
Pulse-rate. Patients whose pulse-rate, per minute, on admission, was—	90 and below	3	1	33·33	2	1	...	...	...
	91—120	40	22	55	4·93	40	28	70	7·98
	121—150	24	17	70·82	3·50	27	17	62·59	6·73
	151 and above	1	1	100	3	...	...	...	...

II—*continued.*

		Control cases.				Treated cases.			
		Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).
II—*contd.*									
Respirations.									
Patients whose respirations, per minute, on admission, were—	35 and less	49	30	62·04	4·60	47	33	70·21	8·83
	36—50	19	11	57·89	3·09	20	12	60	4·12
	51 and above	...	...	...	...	1	...	...	...
Buboes.									
Patients in whom buboes were found, on admission or later on, to be—	Single	...	...	...	...	...	...	...	...
	Maxillary, single.	...	...	...	...	...	...	...	...
	Cervical, single	5	3	60	2·83	1	1	100	1
	Parotid, single	...	...	...	...	2	1	50	2·50
	Axillary, single.	12	8	66·66	2·62	14	8	57 14	10·12
	Iliac, single	...	...	...	...	...	...	...	...
	Inguinal, single.	...	...	...	...	...	...	..	...
Patients in whom buboes were found, on admission or later on, to be—	Femoral, single.	2	2	100	2·50	1	...	...	...
	Others, single	...	...	...	...	...	...	...	...
	Multiple	...	...	...	...	...	...	...	...
	Multiple, neighbouring.	36	23	63·88	3·10	38	28	73·68	5
	Multiple, opposite.	6	2	33·33	10·00	4	1	25	15
	Multiple, scattered.	7	3	42·85	15·33	8	6	75	16·50
	Absent altogether.	...	...	...	...	...	...	...	...
Sex, age, caste, and nationality.									
Both sexes	Males	48	31	64·58	7·97	54	37	68·51	6·68
	Females	20	10	50	3·85	14	8	57·14	11·68

II—*concluded.*

		Control cases.				Treated cases.			
		Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).	Number of patients.	Number of deaths.	Mortality percentage.	Average stay in hospital before death (in days).
II—*concld.*									
Sex, age, caste, and nationality—*contd.* Among the patients there were—	Up to 10 years of age.	8	5	62·50	5	5	2	40	23·25
	11—25 .	37	23	62·16	4·71	36	22	61·11	5·61
	26—45 .	22	12	54·54	3·12	22	17	77·27	8·26
	46 and above	1	1	100	1	5	4	5	7·62
	Hindoos .	53	34	64·15	4·20	51	34	66·66	8·73
	Mahomedans	11	4	36·36	5·87	7	4	57·14	2·62
	Goanese and Native Christians.	4	3	75	1·83	10	7	70	4·71
	Parsis	...	...	...	...	...	...	...	...
	Europeans and Eurasians.	...	...	...	...	...	...	...	...
Microbes in blood. Patients in whom microbes were found to be—	Present on date of admission.	8	8	100	2·12	19	19	100	2·84
	Absent .	52	28	53·86	3·56	41	21	51·21	8·23
	Not examined.	8	5	62·5	11	8	5	62·5	22·80
Patients in whose blood plague bacilli were discovered on date of admission, and who lived after this for—	0 days .	...	...	...	...	...	...	...	...
	1 day .	2	2	100	2	8	8	100	1·25
	2 days .	3	3	100	2·16	3	3	100	2·16
	3 and a few more days.	2	2	100	3·25	8	8	100	4·68
	Recovered .		...	...	...	...	...	...	...

III.

		Control cases.					Treated cases.				
		Number of patients.	Their proportion to total (per cent.).	Number of deaths.	Mortality percentage.	Average extent of increase or decrease.	Number of patients.	Their proportion to total (per cent.).	Number of deaths.	Mortality percentage.	Average extent of increase or decrease.
III.											
Condition of patients after first application of treatment.											
Duration of life.											
Died within 24 hours of admission.	.....	9	13·23	9	100	...	6	8·82	6	100	..
Lived for more than 24 hours	.....	59	86·76	32	54·23	...	62	91·17	39	62·90	...
Temperature.											
Total of patients admitted with 100°F. and over, who lived for more than 24 hours.	.....	48	70·58	29	60·41	...	55	80·88	36	65·45	...
Patients admitted with more than 100°F., in whom the next temperature, examined after treatment (or, in controls, after admission), showed an—	Increase .	27	39·85	19	70·37	1·92	28	41·17	18	64·28	1·12
	Decrease .	27	39·85	16	59·25	1·58	29	42·64	21	72·41	2·03
	Stationary condition.	3	4·41	2	4·41	...	2	2·95	1	50	...
Pulse-rate.											
Total of patients admitted with more than 100 in a minute, who lived for more than 24 hours.	.....	57	83·82	32	47·05	...	60	88·23	37	61·66	...
Patients admitted with more than 100 in a minute, in whom the next examination, after treatment (or, in controls, after admission), showed an—	Increase .	31	45·58	21	67·74	8·22	25	36·76	20	80	8·12
	Decrease .	22	32·35	12	54·54	9·00	29	42·64	16	55·17	14·10
	Stationary condition.	13	19·11	8	53·84	...	11	16·17	6	54·54	...
Respirations.											
Total of patients admitted with more than 28 in a minute, who lived for more than 24 hours.	.....	50	73·52	26	52	...	59	86·76	26	44·06	...
Patients admitted with more than 28 in a minute, in whom the next examination, after treatment (or, in controls, after admission), showed an—	Increase .	19	27·94	14	73·68	5·10	20	29·55	16	80	5
	Decrease .	28	41·17	14	50	3·32	26	38·23	12	46·15	6·03
	Stationary condition.	12	17·64	7	58·3	...	16	23·52	8	50	...

IV.

		Control cases.				Treated cases.			
		Number of patients.	Their proportion to total (per cent.).	Number of deaths.	Mortality percentage.	Number of patients.	Their proportion to total (per cent.)	Number of deaths.	Mortality percentage.
IV. *Condition of patients throughout the treatment.*									
Temperature.									
Patients admitted with more than 100°F., who lived for more than 48 hours, and in whom the temperature, after the first application of treatment (or, in controls, after admission), reached maximum.	Within 24 hours.	28	41·17	16	57·14	27	39·85	15	55·55
	Later than 24 hours.	13	19·11	10	76·92	18	26·47	12	66·66
Pulse-rate.									
Patients admitted with more than 100 in a minute, who lived for more than 48 hours, and in whom the rate, after first application of treatment (or, in controls, after admission), reached the maximum.	Within 24 hours.	31	45·58	12	38·70	27	39·85	11	40·74
	Later than 24 hours.	16	23·52	10	62·50	24	35·29	18	75
Respirations.									
Patients admitted with more than 28 per minute, who lived for more than 48 hours, and in whom the rate, after first application of treatment (or, in controls, after admission), reached a maximum.	Within 24 hours.	24	35·29	9	37·50	21	30·88	8	38·09
	Later than 24 hours.	23	33·82	15	65·21	28	44·17	17	60·71
Temperature.									
Patients who ultimately recovered, and who, after their temperature had reached normal, had a rise to above 99°F. within a fortnight of their admission.	...	14	20·58	...	...	16	23·52	...	...

V.

Additional Information :—(1) The highest temperature, pulse and respiration of all recovery cases (treated and control).

Control cases.			Treated cases.		
Temperature.	Pulse.	Respirations.	Temperature.	Pulse.	Respirations.
102·6	128	36	104·2	130	58
103	142	44	104	112	30
104	140	46	102·8	130	48
103	160	46	103	28	25
104·6	130	35	103	110	40
103·8	128	38	103·6	120	28
103·8	120	33	102	132	48
102·8	122	35	103·8	122	30
101·2	110	26	104·2	130	42
104·2	140	46	104	112	30
100	104	28	104·8	160	45
103·2	122	34	103·8	120	30
104	160	50	104·6	140	38
101·4	112	28	105·8	140	45
103·8	120	34	104	126	30
104	120	30	104	120	30
103	120	44	103·4	110	30
100	128	38	103·6	130	34
101·6	128	35	103	128	35
103	130	35	104·9	120	40
103·6	120	36	105	140	40
102·8	110	28	102	124	35
103	122	26	102	122	40
102·8	122	33	...	...	...
104	130	36	...	...	...
100	98	24	...	...	...
104·2	144	40	...	...	...

(2) *The time (in days) when (1) temperature, (2) pulse, and (3) respirations became for the first time normal, after the application of treatment or admission into hospital (in days).*

Control cases.			Treated cases.		
Temperature.	Pulse.	Respirations.	Temperature.	Pulse.	Respirations.
8·42	9·20	9·02	6·24	8·40	7·04

(3) *Average stay in hospital of fatal cases (in days).*

Control cases.	Treated cases.
4·19	7·59

APPENDIX A.

Method of preparation of Lustig's Anti-Plague Serum, as employed by Drs. G. Polverini and A. Mayr in the Bombay Municipal Laboratory at Parel, until May 1902.
By A. Mayr, M.D.

1. Cultures of B. *pestis* were made from the blood of plague patients. These were grown on the ordinary 1 per cent. peptone agar in large glass dishes (10″ diameter) for 2—3 days.

2. After macro-, and micro-scopical examination to ascertain the purity of the growth, it was scraped off with a spatula and transferred to a glass beaker.

3. The mass obtained from the scrapings of 5 or 6 dishes was then mixed with about 100 c.c. of a one per cent. solution of caustic potash, and the whole well stirred until a uniform mucilaginous solution was obtained. This was kept standing for half an hour to make sure of its sterility, which was always controlled by culture at this stage.

4. To this was added with constant stirring one per cent. of acetic acid, until a white flocculent precipitate was brought down. This was collected on a filter and washed till free from acid. This precipitate which can be dried and kept for a considerable time without deterioration, is the *immunising substance*, and is soluble in one per cent. sodium carbonate solution.

5. When required for the immunisation of the horses, the *immunising substance* (in most cases still moist) was dissolved in some sodium carbonate solution, and to this was added as much 0·6 per cent. salt solution as would approximately make a concentration of 1 gramme of dried *immunising substance* in 2,000 c.c. of fluid, for injection.

The amount of moist *immunising substance* required was known by experience, but in order to calculate more exactly what the concentration was, 10 c.c. of the fluid, as used to inject the horses, was placed in a graduated measure glass, and mixed with 5 c.c. of the following solution:—

Mercuric chloride	7·0
Hydrochloric acid	5·0
Distilled water	100·0

This brought the *immunising substance* down again in the form of a white precipitate, which on settling could be measured in the graduated glass. From the height to which the *immunising substance* filled the glass, it was possible to calculate its weight in the dried state from a table which had been worked out once for all.

6. One hundred c.c. of fluid for injection, equal to 0·05 gramme of dried *immunising substance*, was usually injected into a horse subcutaneously the first time; and the injections were repeated about once a fortnight, the amount of *immunising substance* being increased by about 2—3 centigrammes each time.

The serum was tested on animals from time to time, during the process of immunisation, and when found sufficiently active, the horse was bled. A horse was considered ready for bleeding when 0·5 c.c. of serum protected a guinea pig of medium weight against an infection from which the control animal died in 4—5 days. This standard was based

on the experience that serum of such activity showed decided curative effects in plague patients in doses of about 60 c.c.

The serum was neither sterilised nor was an antiseptic added to it, but its sterility was controlled bacteriologically and its innocuity by injection in white mice before issue.

Every thing used for the preparation of the serum was of course sterilised.

APPENDIX B.

Abstract of an unpublished paper by Captain E. D. W. Greig, M.B., B.Sc., Edin., I.M.S., "On the Infection of the Blood in Bubonic Plague" (From the Plague Research Laboratory, Parel, Bombay, 18th June 1902).

Object of the research :—To ascertain—

(*a*) The frequency of blood infection in ordinary cases of bubonic plague.

(*b*) The effect of such invasion on the case mortality.

(*c*) Whether the invasion takes place early in the disease, or only just prior to death.

Plan of work :—The observations were made in cases on the first day of their admission to hospital. No case was examined which had been more than three days ill. The site of bubo and termination of the case was noted.

One c.c. of blood was taken from a superficial vein in each case, by means of a sterilised syringe. The blood was at once transferred to a flask containing 50 c.c. of sterile bouillon, so that it was diluted 50 times. In this way the effects of any bactericidal substances in the blood were lessened. The flasks were kept in the laboratory at room temperature (about 28° to 29° cent.), and the appearance of stalactite growth looked for.

From the flasks sub-cultures were made on dry agar, and the growth tested in the usual ways. In a certain number of instances the virulence of the growth was tested by inoculation of monkeys, rats or guinea-pigs. "A similar method was employed by Castellani to determine the presence of bacillus typhosus in the blood of typhoid fever cases." (Centralblatt für Bact. Bd. XXXI, No. 10.)

The result of this investigation was as follows :—

The number of patients examined was 132, of which number 79 had plague bacilli in the blood, or a percentage of 59·8. Of these 79 cases, 77 died, a case mortality of 97·6 per cent. On the other hand, the remaining cases, 53 in number, in which the blood was sterile at the time of examination, showed a case mortality of 44·1 per cent. only. Of the 79 blood-infected cases, 26 were examined on the first day of illness, 27 on the second, and 20 on the third day.

The length of life of a patient subsequent to the invasion of his blood by plague bacilli, and therefore probably the time during which there is danger of his spreading the infection, may be roughly gauged from the following statement :—Ten cases died within 12 hours of the discovery of the bacillus in the blood; 24 cases died within 24 hours; 15 cases within two days; 19 cases within three days; 3 cases within four days; 4 cases within five days; one case within seven days; and one within nine days. The above shows that in the severe cases of ordinary bubonic plague invasion of the blood occurs very early

and greatly increases the gravity of the prognosis; and that there is really no distinction to be drawn between bubonic and septicæmic plague, the one type merging into the other.

A further interesting point is the varying length of time patients live after the appearance of plague germs in their blood. This may be ascribed to a variation in the bactericidal power of the blood in different individuals. Wright (Lancet, March 22, 1901) has shown that human blood usually exhibits little or no bactericidal power towards the plague bacillus, and this may serve to explain the fatal nature of septicæmic cases in this disease.

The following are briefly the conclusions to be drawn from the above research : –

(1) That blood infection is more frequent than has been supposed in ordinary cases of bubonic plague, and averages 60 per cent.

(2) That the case mortality of such cases is extremely high, about 98 per cent.

(3) That the blood invasion, in most cases, occurs at an early date in the disease.

(4) That the lymphatic glands present little or no obstacle to the invasion of the blood stream by the bacilli.

(5) That the period between the time of invasion of the blood and the death of the patient is longer than was previously believed.

(*NEW SERIES.*)

No. 20.

SCIENTIFIC MEMOIRS

BY

OFFICERS OF THE MEDICAL AND SANITARY DEPARTMENTS

OF THE

GOVERNMENT OF INDIA.

SERUM-THERAPY OF PLAGUE IN INDIA;

REPORTS BY Mr. W. M. HAFFKINE, C.I.E., AND VARIOUS OFFICERS OF THE PLAGUE RESEARCH LABORATORY, BOMBAY.

EDITED WITH AN INTRODUCTION

BY

LIEUT.-COL. W. B. BANNERMAN, M.D., B.Sc., F.R.S.E., I.M.S.,
Director, Plague Research Laboratory, Bombay.

ISSUED UNDER THE AUTHORITY OF THE GOVERNMENT OF INDIA BY THE SANITARY COMMISSIONER WITH THE GOVERNMENT OF INDIA, SIMLA.

CALCUTTA:
OFFICE OF THE SUPERINTENDENT OF GOVERNMENT PRINTING, INDIA.
1905.